A systematic approach to managing symptoms related to advanced oncological illness can improve patient quality of life and lessen distress.

Palliative Pharmacotherapy: State-of-the-Art Management of Symptoms in Patients With Cancer

Eric E. Prommer, MD

Background: Advanced cancer produces multiple symptoms as patients progress through their disease trajectory. Identifying, measuring, and providing therapy for uncontrolled symptoms becomes important because disease-altering therapies may be no longer possible. Symptoms other than pain that cause distress in patients with cancer include delirium, dyspnea, anorexia, nausea, and fatigue. Precise management of these symptoms can lead to the best possible quality of life and lessen distress. This article reviews current management strategies of these symptoms.

Methods: The epidemiology, mechanisms, assessment, and therapies of common symptoms in the advanced cancer population are reviewed.

Results: Identifiable approaches facilitate symptom management in advanced illness.

Conclusions: Using a systematic approach to symptoms in advanced illness can improve the quality of life and lessen distress among patients with cancer and their families, friends, and caregivers.

Delirium

Delirium is a clinical emergency characterized by changes in consciousness, hallucinations, and changes in the sleep–wake cycle and language. Delirium is a frequent event in patients with advanced cancer, and factors predisposing patients with advanced cancer include drugs, infection, brain metastasis, and underlying dementia. Delirium differs from dementia in that dementia does not have acute alterations in consciousness. Delirium is classified according to level of agitation; for example, a patient who is agitated has hyperactive delirium and a patient who is withdrawn and somnolent has hypoactive delirium. Patients usually have mixed features. Prevalence rates for delirium range from 30% to 50% for hospitalized patients and is typical in the hours or days before death. Experiencing delirium is likely to cause distress in families. Patients who are delirious are unable to communicate levels of pain or other symptoms and cannot take part in health care decisions. Although delirium is often a harbinger of a poor prognosis, it is reversible in 50% of cases. Health care professionals use nonpharmacological as well as pharmacological interventions to treat delirium. Nonpharmacological approaches to delirium include using clocks to show the time, lighting the room, and frequent reorientation, whereas pharmacological interventions may include the use of antipsychotic medications, which can be used to palliate
patients who are agitated (hyperactive delirium) as well as those experiencing hallucinations regardless of agitation level.

**Mechanisms**

Delirium results from underlying disorders that cause imbalances in brain neurotransmitters. Neurotransmitters involved in delirium include dopamine, glutamate, norepinephrine, acetylcholine, γ-aminobutyric acid, and serotonin. Cytokines (interleukin [IL]-1, IL-2, tumor necrosis factor [TNF], interferon) produced by the immune system, the tumor, or cancer treatment may mediate central nervous system effects, such as somnolence, agitation, and cognitive failure. Drug therapies for delirium target imbalances in neurotransmitters, which may play a role in developing delirium.

**Assessment**

A history of the patient’s baseline mental status prior to symptom onset should be obtained from his or her family, caregivers, or both parties. Fluctuating consciousness is the hallmark of delirium. Assessment tools can screen or rate delirium or do both. Commonly used tools include those for screening (Mini Mental State Examination, Confusion Assessment Method) or rating of severity (Memorial Delirium Assessment Scale, Disability Rating Scale). Some instruments will address more than 1 goal. Other important considerations are time constraints, the level of expertise and training of the investigator (the Mini Mental State Examination requires none), and constraints of the patient (eg, patient in the intensive care unit).10

**Management**

**Nonpharmacological:** Identification of reversible causes is important. Investigations should be tailored to each individual patient’s goals of care because 50% of cases of delirium may be reversible.7 Health care professionals must look for infection, dehydration, and drug and metabolic abnormalities as potentially reversible causes of delirium. Patients with cancer should be evaluated for central nervous system metastasis. It is worth noting that fecal impaction and urinary tract infection are often overlooked as causes of delirium. Common drugs linked to delirium include opioids, anticholinergics, benzodiazepines steroids, and select chemotherapy agents. Inquiring about alcohol intake is prudent because alcohol withdrawal can precipitate delirium and responds to benzodiazepines. Nonpharmacological approaches to delirium include keeping room lights on, having calendars and pictures at the bedside, frequent redirection, and allowing patients to participate in their care.11

**Pharmacological:** Antipsychotic drugs are the primary therapy for all forms of delirium, in particular hyperactive and mixed delirium.12 Table 1 reviews common agents used for delirium.13 Haloperidol remains the gold standard despite a paucity of clinical trials.14 Severity of delirium and patient age are both important considerations for dosing. In elderly patients (aged ≥ 60 years) and in patients with mild to moderate agitation, Canadian guidelines suggest that haloperidol be started at low doses (ie, 0.5 mg orally 2–3 times a day) and then be titrated to obtain an effect.15 Severe cases and younger patients may require more haloperidol, and, in severely agitated patients, rapid dosing is required. In this setting, parenteral doses are recommended and haloperidol doses such as 1 to 2 mg in young patients and 0.25 to 0.5 mg in elderly patients, repeated every 1 to 2 hours until the agitation resolves; protocols for rapid titration are available.16 Haloperidol is the least sedating of the antipsychotic class and can be intravenously or orally given.17

Atypical antipsychotics may also be useful because they are less likely to cause extrapyramidal symptoms and have less potential for effects on cardiac conduction; however, these antipsychotics cannot be given via the parenteral route.18 Commonly used atypical antipsychotics include olanzapine, quetiapine, and risperidone. These types of antipsychotics are also appropriate for patients with underlying Parkinson disease.

Benzodiazepines are not indicated for the management of delirium and are best used in the setting of de-
lirium associated with alcohol withdrawal. Benzodiazepines can be added to haloperidol when agitation does not respond to haloperidol alone.

**Chronic Nausea and Vomiting Unrelated to Chemotherapy**

Nausea and vomiting affects up to 70% of patients with advanced cancer; however, nausea is more common. Chronic nausea is defined as nausea that lasting more than 1 week without an identifiable precipitant, and its causes include underlying cancer and its progressive effects as well as medication use (eg, opioids).

**Mechanisms**

The nausea and vomiting reflex is governed by nuclei in the medulla. The nucleus tractus solitarius receives input from multiple sites, and then relays to the dorsal motor nucleus of the vagus to cause vomiting. Afferent input comes from the chemoreceptor trigger zone, vagus nerve, cortex, and vestibular pathways. Neurotransmitters populate these areas critical to the emetic reflex and include dopamine, serotonin, histamine, substance P, and acetylcholine. Blocking these neurotransmitters forms the basis for antiemetic therapy.

**Assessment**

Health care professionals should gather information about duration, frequency of vomiting episodes, and the ability of the patient to keep fluids down — all of which may affect the route of drug administration. Delayed nausea and vomiting due to chemotherapy should be considered. Large-volume emesis suggests gastric or bowel obstruction, whereas polydipsia, polyuria, and cognitive changes suggest metabolic causes. Health care professionals should inquire about the presence of constipation, which can also cause nausea. Mood should be assessed. Physical examination findings may provide clues. Papilledema suggests brain metastasis, whereas orthostatic changes suggest autonomic insufficiency. Numerical rating scales can be used to measure the severity of nausea.

**Management**

Recommendations support either antiemetic therapy based on proposed pathophysiology or a sequential trial of antiemetics. Response rates near 80% with these approaches. Table 2 lists select antiemetics that can be used in patients with advanced illness. 

**Nonpharmacological:** Operative approaches are considered in cases of mechanical bowel obstruction. However, consideration for surgical interventions should be individualized, with health care professionals weighing the risks and benefits of the procedure. Use of acupuncture to treat nausea and vomiting in advanced illness has not been evaluated.

**Dyspnea**

Dyspnea is the uncomfortable awareness of breathing, and it is a frequent symptom in advanced illness with prognostic importance. The prevalence of dyspnea is between 20% and 80% in patients with advanced cancer. It has been described in various ways, including as air hunger, suffocation, and choking. Health care professionals typically have differing perspectives on dyspnea, and they often under-rate it as a symptom.

**Mechanisms**

Peripheral receptors involved in breathing play a role in the perception of dyspnea. Excessive input from receptors sensing oxygen and carbon dioxide levels contribute to dyspnea. The overactivity of mechano-receptors and respiratory muscle as well as lung and chest-wall receptors all contribute to the sensation of dyspnea. These receptors likely also stimulate the cortex, thus influencing cortical perception.

**Assessment**

Many tools exist to measure breathlessness, but few

<table>
<thead>
<tr>
<th>Drug</th>
<th>Dosage</th>
<th>Route</th>
<th>Comment</th>
</tr>
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<tbody>
<tr>
<td>Butyrophenone</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Haloperidol</td>
<td>0.5–2.0 mg every 4–6 h</td>
<td>Intravenous</td>
<td>Useful with associated delirium</td>
</tr>
<tr>
<td>Metoclopramide</td>
<td>10 mg every 6 h</td>
<td>Intravenous</td>
<td>Prokinetic</td>
</tr>
<tr>
<td>Antihistamine</td>
<td></td>
<td>Oral</td>
<td>For vestibular component</td>
</tr>
<tr>
<td>Cannabinoids</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Dronabinol</td>
<td>5 mg/m² every 6 h</td>
<td>Oral</td>
<td>Very long half-life (≤ 56 h)</td>
</tr>
<tr>
<td>Nabilone</td>
<td>1–2 mg twice daily</td>
<td>Oral</td>
<td>2-h half-life Not detected on urine testing</td>
</tr>
<tr>
<td>Glucocorticoid</td>
<td>Brain metastasis: 4–6 mg every 6 h</td>
<td>Intravenous Oral</td>
<td></td>
</tr>
</tbody>
</table>

**Atypical Antipsychotic**

Olanzapine 2.5–7.5 mg daily Oral Single daily dose May require another antiemetic for breakthrough emesis

Information from reference 21.
cancer-specific tools exist; however, one such tool is the Lung Cancer Symptom Scale, and a scale, such as the visual analog scale, numerical pain scale, or cancer-specific tool, is recommended.32,33

**Management**

In advanced illness, treatment should focus on comfort and should include assessment of overall patient distress and work of breathing. Reversible causes of dyspnea and their treatment should be in keeping with the individual patient’s goals of care.

**Oxygen Therapy:** Oxygen therapy can benefit patients with chronic obstructive pulmonary disease and hypoxia in domains such as exercise capacity, cognitive function, and survival; however, its benefits are not clear in the oncology setting.34 Oftentimes, patients with cancer are dyspneic but not hypoxemic. Randomized controlled trials have compared oxygen therapy with room air for relief of dyspnea.35,36 The results of 2 studies suggested that those with cancer who were hypoxemic on room air benefited from oxygen, and the results of another study showed that oxygen did not benefit those with cancer experiencing dyspnea who were not hypoxemic.36,37

**Opioids:** Opioids are the preferred treatment for refractory dyspnea, and patients typically benefit from oral or parenteral opioids.38 Sustained-release formulations are effective.39 All opioids as a class are effective for dyspnea because they decrease the perception of breathlessness. Results from a meta-analysis of 9 small, randomized studies (116 study patients) and 1 randomized crossover trial (48 study outpatients) showed that systemic opioids reduced mean chronic breathlessness by approximately 20% over baseline.40 No evidence suggests that nebulized opioids are effective.41

**Benzodiazepines:** Benzodiazepines are used for dyspnea and to relieve anxiety.42 Results from a meta-analysis of 7 studies (200 study patients) found that benzodiazepines did not relieve breathlessness and instead increased the risk of drowsiness; however, the studies were heterogeneous and the sample sizes were small.43 One controlled trial found that adding subcutaneous midazolam to an opioid enhanced dyspnea relief in patients with advanced cancer.44

**Antidepressants:** Current evidence for the use of antidepressants to decrease breathlessness is inconsistent.45

**Saline:** A randomized, single-blinded trial of 40 people with an exacerbation of chronic obstructive pulmonary disease showed no consistent relief of breathlessness from nebulized, isotonic saline compared with placebo.46

**Furosemide:** Exploratory studies are conflicting regarding the efficacy of inhaled furosemide on breathlessness.47 Thus, the level of efficacy of furosemide in this patient population requires confirmation in larger clinical trials.

**Cancer Anorexia/Cachexia**

Cancer anorexia/cachexia is defined as “a multifactorial syndrome defined by ongoing loss of skeletal mass (with or without loss of fat) that cannot be reversed by conventional nutritional support and leads to progressive functional impairment.”48 A cluster of symptoms characterizes the syndrome and includes weakness, early satiety, and anorexia.48 Criteria for diagnosing cachexia in patients with cancer are: weight loss of more than 5% in 6 months (in the absence of starvation), body mass index below 20 kg/m², and any degree of weight loss of more than 2% or appendicular skeletal muscle index consisting of sarcopenia (men: < 7.26 kg/m²; women: < 5.45 kg/m²).49 It has 3 stages: precachexia, cachexia, and refractory cachexia. The syndrome occurs in 50% of patients with cancer (many various types).49

Associated complications include poor performance status, poor quality of life, decreased survival, and poor response and tolerability to chemotherapy.48-50 Anorexia frequently accompanies the syndrome.51 Patients may manifest decreased muscle mass and decreased strength, and they may experience fluctuations in resting energy expenditure and increased psychosocial distress.52 Both lean body mass and muscle strength, as measured by handgrip strength, are predictive of survival and quality of life.53

Cancer anorexia/cachexia limits therapeutic options.54 Weight loss correlates with treatment toxicity, poor tumor response, and lower chemotherapy response rates.55 Loss of more than 10% of premorbid weight before chemotherapy predicts death and is independent of disease stage, tumor histology, and performance status.55 Anorexia is also a powerful predictor of early death, and this observation persists even after adjusting for several other prognostic parameters.56 Thus, both weight loss and anorexia predict poor prognosis for patients with advanced cancer.

**Mechanisms**

The mechanisms leading to the development of cancer anorexia/cachexia are not fully understood. Anorexia/cachexia results from abnormal host responses to cancer, and the syndrome appears to result from the interplay between tumor byproducts and host cytokine response.57,58 In animal studies, targeting cytokines with monoclonal antibodies relieves cachexia.59 The interplay between tumor byproducts and inflammatory mediators creates acute-phase proteins in the liver, and this, in turn, leads to the breakdown of muscle protein, lipolysis of fat, insulin resistance, and an elevated level of triglycerides.60 Inflammatory mediators enter the hypothalamus,
which is where they mimic anorexigenic neurotransmitters and cause anorexia.60

**Assessment**

Tools measuring cancer anorexia/cachexia include the Edmonton Symptom Assessment System, Bristol Meyers Anorexia/Cachexia Recovery Instrument, Patient Generated Global Assessment Instrument, and the cancer anorexia/cachexia subdomain of the Functional Assessment of Anorexia/Cachexia Therapy questionnaire.61-63 Clinical tools useful for assessment cancer anorexia/cachexia include weight, midarm circumference, and hand grip.61 It is worth noting that mid-arm circumference has prognostic value.64 Optimal methodology to assess muscle mass has not yet been determined. Computed tomography, dual energy x-ray imaging, and bioimpedance can all be used to measure muscle mass.48 Whole-body impedance and electroconductivity are based on the principle that lean tissue conducts electricity better than fat.

**Management**

Secondary reasons for weight loss should be addressed or ruled out. Health care professionals should look for nausea, constipation, taste alteration, depression, dyspnea, and deconditioning as possible causes. Other important patient factors contributing to cancer anorexia/cachexia include dry mouth, difficulty swallowing, any alteration in sense of smell, early satiety, mouth sores, dental issues, and anxiety.

**Nutritional Support:** Nutritional support early on is important and can include dietary advice, nutritional supplements, and consideration of an enteral diet. Dietitians may recommend foods tailored to preference, portions, and an individual patient’s ability to swallow. Pungent foods should be avoided. It is not clear whether nutritional supplements reverse weight loss and decline in quality of life.65

**Psychosocial Intervention:** Psychosocial interventions are important because patients and their friends, families, and caregivers may be experiencing distress. Information, support, and clinician interactions with the patient and his or her friends, family, and caregiver can help mitigate such distress.

**Pharmacologic Intervention**

**Megestrol:** Megestrol acetate has long been an option for cancer anorexia/cachexia.66 Results of the initial study (and subsequent studies) showed significant improvement over placebo with respect to appetite, nausea, weight gain, and food intake (megestrol acetate 800 mg/day).67 Bruera et al68 conducted a 15-day, blinded, placebo-controlled, crossover trial of megestrol acetate 480 mg/day and found statistically significant improvements in caloric intake, appetite, and weight gain among the study participants. Results of a meta-analysis that included 3,500 participants and 25 clinical trials comparing megestrol acetate with steroids, nandrolone, eicosapentanoic acid, and dronabinol suggested consistent improvement in appetite, weight gain, and quality of life.69 Megestrol acetate improves appetite and weight gain in approximately 30% of patients.69 The numbers of patients needed to treat are 8 patients for weight gain and 3 patients for anorexia.69 Megestrol acetate benefits patients with HIV/AIDS and geriatric cachexia.70,71 Adverse events that occur relatively infrequently include adrenal insufficiency, thrombosis, and hyperglycemia.72-74 Rash and menstrual disorders have similar frequency.57,75 Some evidence suggests that the drug improves fat-free body mass.71

**Glucocorticoids:** Glucocorticoids work by inhibiting markers of inflammation and also increase neuropeptide Y.70 Glucocorticoids, such as dexamethasone (3–6 mg/day), prednisone (15 mg/day), and methylprednisone (32 mg/day), can improve appetite and can cause weight gain.77 Their effects are rapid but are of short duration than megestrol acetate.79 Glucocorticoids can be used for patients in need of a rapid effect but are more appropriately used in patients with a short prognosis.

**Cannabinoids:** Dronabinol is the most-studied cannabinoid, with dosages ranging from 2.5 to 20 mg/day; compared with placebo, dronabinol reduces nausea, stabilizes weight, and increases appetite.79 Cannabinoids probably inhibit inflammatory mediators, and they also may influence leptin by activating the cannabinoid receptor. Toxicities include euphoria, hallucinations, tachycardia, and psychosis.79 A phase 2 study (N = 19) found that 5 mg/day dronabinol improved anorexia in 68% of study patients, but 16% of study patients discontinued the drug due to adverse events.79 With respect to appetite and weight gain, dronabinol is inferior to megestrol acetate and megestrol acetate/dronabinol combinations, and it is not recommended for cancer anorexia/cachexia.80,81

**Anamorelin:** Anamorelin is a novel, ghrelin, growth-hormone secretagogue taken orally for the treatment of cancer anorexia/cachexia because it improves appetite and muscle mass.82 Ghrelin is an orexigenic hormone that stimulates food intake in a dose-dependent manner in rodents and humans by stimulating growth hormone and neurotransmitters such as neuropeptide Y.83,84,85 Levels of ghrelin are elevated in fasting and reduced in obesity.86 It also stimulates the hypothalamus, thus causing food intake.87 The results of a phase 3 trial showed increased lean body mass and decreased symptoms of anorexia/cachexia in patients with stage 3/4 non–small-cell lung cancer.85

**Nonsteroidal Anti-Inflammatory Drugs:** Nonsteroidal anti-inflammatory drugs (NSAIDs), including cyclooxygenase 2 inhibitors, reduce the tumor-assoc-
associated release of acute-phase reactants and cytokines. The results of 2 controlled clinical trials of patients with cancer anorexia/cachexia suggested that NSAIDs were effective for gaining weight and muscle mass in this study population, and this was especially true when NSAIDs were combined with progestogens.88,89 However, larger trials are required to further study their effect in this patient population.88,89

**Thalidomide:** Thalidomide has multiple immune-modulating, anti-inflammatory, and TNF-α and IL-6–inhibiting properties. The results of 2 controlled clinical trials show that it increased appetite, weight, and feeling of well being in study patients with cancer anorexia/cachexia.90,91 These initial results are promising, but they may need to be confirmed by additional clinical trials.90,91

**Melatonin:** Melatonin is an endogenous hormone secreted by the pineal gland and is used to treat sleep disorders. It inhibits cytokines and TNF-α. Two controlled clinical trials measuring the efficacy of melatonin in 1,600 study patients with advanced cancer found improvements in asthenia and anorexia compared with placebo.92,93 However, another controlled clinical trial comparing melatonin with placebo in study patients with cancer anorexia/cachexia (N = 48) did not find any differences between the 2 treatment groups.92 Thus, more studies are indicated to determine its effectiveness.

**Anabolic Steroids:** Oxymetholone, oxandrolone, nandrolone, and fluoxymesterone are anabolic steroids studied in cancer anorexia/cachexia. They act to increase muscle mass without changes in appetite or amount of food intake. They have been evaluated for cachexia with a nononcological origin (eg, AIDS, chronic obstructive pulmonary disease, renal impairment).94-96 One controlled clinical trial confirmed that the efficacy of fluoxymesterone in cancer anorexia/cachexia was comparable with that of megestrol acetate. However, its use is not recommended due to its high rate of hepatotoxicity.78

**Combination Treatment:** Another approach to cancer anorexia/cachexia is using multiple drugs on different pathways that play a role in the disorder. A controlled clinical trial compared 5 treatments (megestrol acetate, eicosapentaenoic acid, L-carnitine, thalidomide, and combination megestrol acetate/eicosapentaenoic acid/L-carnitine/thalidomide) during a 4-month period.95 The results showed that the drug combination was superior to the drugs alone and improved appetite and asthenia, reduced energy expenditure at rest, increased fat-free mass, and reduced IL-6.95

**Fatigue**

Patients with cancer commonly experience fatigue, which impacts the physical, emotional, and cognitive domains.97,98 Fatigue can impair concentration, often manifesting as lack of motivation.61 In addition, patients may perceive fatigue as decreased energy and weakness.61 Use of radiation, chemotherapy, biological therapies, and targeted therapies may cause fatigue.99,100 Moreover, fatigue can persist in cancer survivors and last for many years.101

**Mechanisms**

Factors contributing to fatigue in patients with cancer can include tumor burden, oncology treatment, and the effect of cytokines.61 Cytokine production leads to symptoms of fever, pain, cachexia, and depression. Patient comorbidities can also exacerbate fatigue and may include chronic obstructive pulmonary disease, renal insufficiency, and electrolyte, endocrine, and pre-existing mood disorders.61

**Assessment**

Fatigue should be evaluated like any other symptom, with the health care professional detailing its severity, temporal features, any exacerbating and alleviating factors, associated distress, and its impact on the patient's daily life. Tools for the measurement of fatigue include the Edmonton Symptom Assessment System, the Functional Assessment of Cancer Therapy-Fatigue Subscale, the Brief Fatigue Inventory, and the Memorial Symptom Assessment Scale Short-Form.102

**Management**

Health care professionals can use nonpharmacological and pharmacological approaches to treat cancer-related fatigue. Identification of anemia, infection, hypogonadism, pain, depression, anxiety, cachexia, dehydration, metabolic abnormalities, other comorbidities, and medication use, as well as autonomic insufficiency and their attempted correction, are also important. Clear relationships exist between hemoglobin levels and symptoms of fatigue and functional and physical well-being.103 Treating anemia does improve energy and quality of life; however, transfusions can benefit patients with cancer approximately 60% of the time.103,104 Erythropoietin and other similar treatments are impractical in patients with advanced cancer because these treatments often take 4 to 8 weeks.104 As the disease progresses, the benefits of transfusions lessen.104

**Nonpharmacological:** Exercise can be beneficial for cancer-related fatigue because it improves cardiovascular conditioning, helps patients maintain muscle mass, and can improve mood and sleep.105 Exercise can also benefit patients receiving chemotherapy and bone marrow transplants.106 However, it is important for the health care professional to set realistic expectations for patients when recommending exercise. Patients with cancer may experience metabolic changes, such as an excess lactate level, and morphological muscle changes, such as myofibrillar and sarcromeric abnormalities, even in tumor-free muscles.107-109 Decondition-
ing complicates exercise goals, and use of steroids can cause physical weakness. Thus, an ideal exercise program appropriate for all degrees of performance status among patients with advanced illness remains to be determined.

Pharmacological: Management options for cancer-related fatigue include corticosteroids and psychostimulants. Glucocorticoids have been shown to improve fatigue in advanced illness, although their benefits are short term. Steroids are best reserved for patients with a short prognosis. Doses equivalent to dexamethasone 8 mg daily are appropriate. A meta-analysis of psychostimulants for cancer-related fatigue suggested a benefit for this patient population. Psychostimulants such as methylphenidate and modafinil can also be used.

Conclusions
Symptom management in patients with advanced cancer is more effective when health care professionals use a systematic approach to assessment. Expert management requires understanding of the pathophysiology of common symptoms in advanced cancer, use of symptom assessment tools to measure symptom intensity, and the application of proven symptom control interventions.

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