Palliative Care Symptom Management Guidelines

Dana-Farber Cancer Institute/ Brigham & Women's Hospital

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Dana-Farber Cancer Institute/Brigham and Women's Hospital Palliative Care Management Guidelines "Orange Book" provides educational information for healthcare professionals at Dana-Farber and Brigham and Women's Hospital. This information is not medical advice. The "Orange Book" is not continually updated, and new safety information may emerge after the most recent publication date. Health care providers should always exercise their own independent clinical judgment and consult other relevant and up-to-date experts and resources. Official prescribing information should be consulted before any product is used or recommendation made.

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Introduction

This “Orange Book” is a reference pocketbook intended to provide palliative care symptom management guidelines to Dana-Farber Cancer Institute (DFCI) and Brigham and Women’s Hospital (BWH) clinicians and learners. It is not a comprehensive guide and does not serve as a replacement to primary literature and expert consultation. The “Orange Book” intentionally does not include guidance on pain management and nausea/vomiting symptom management; those topics have separate pocketbooks titled Pain Management Guidelines “Pink Book” and Chemotherapy Induced Nausea/Vomiting Guidelines “Green Book”. All three pocketbooks can be found online at pinkbook.dfci.org.

Important Definitions

Palliative Care: Palliative care focuses on providing relief from all sources of suffering associated with serious illness, including physical, psychological, social, spiritual, and existential suffering. This focus of care extends to both patient and family. Palliative care is provided by an interprofessional team that works with patients and their clinicians. The interprofessional team often consists of nurses, nurse practitioners, social workers, chaplains, pharmacists, physician assistants, physicians, and foreign language interpreters as needed. Palliative care is appropriate for patients of any age and in any stage of serious illness and can be provided along with curative treatment.

Palliative Care Services at DFCI/BWH are provided in these 3 practice settings –

1) Inpatient Palliative Care Consult Service: Several inpatient consult teams care for patients in Brigham and Women’s Hospital and the DFCI Inpatient Hospital, providing recommendations to the inpatient primary team. These teams include:
    - Oncology – patients living with cancer
    - HeartPal – specialty aligned palliative care for patients living with advanced heart disease
    - KidneyPal – specialty aligned palliative care for patients living with kidney disease
    - Other non-oncology – patients living with any other serious illness

2) Inpatient Palliative Care Unit (IPCU): An inpatient unit located in Brigham and Women’s Hospital for DFCI patients with cancer and a high symptom burden. Patients can receive care on the IPCU regardless of prognosis, goals of care, or code status.

3) Outpatient Adult Palliative Care Clinic: There are several outpatient clinics that provide longitudinal ambulatory palliative care:
    - DFCI Oncology at Longwood, Chestnut Hill, Londonderry, Merrimack Valley, Foxborough, and Milford
    - HeartPal at BWH
    - KidneyPal at BWH

Hospice: A program that provides care to people who are thought to be within 6 months of the end-of-life and have stopped treatment for their disease. Hospice aims to control pain and other symptoms of illness, and offers physical, emotional, social, and spiritual support for patients and their families. Hospice care can be delivered in the home, hospice house, hospital (GIP), or nursing home.

General Inpatient Hospice Care (GIP): An inpatient care plan for a hospice patient who has short-term symptom management needs that cannot be provided adequately in any other setting. Patients who no longer qualify for GIP because their symptoms can be controlled in another setting can receive hospice care in that other setting, e.g., home or nursing home.

References: Important definition’s list of references can be found on page 22.

Appetite Stimulation in Cancer-Related Anorexia Cachexia Syndrome (CACS)

Ben Kematick, PharmD

Description: Anorexia-Cachexia is a broad, multi-organ syndrome present in multiple chronic diseases. Cachexia is characterized by loss of appetite, weight, and skeletal muscle, leading to fatigue, functional impairment, increased treatment related toxicity, poor quality of life, and reduced survival. Cachexia is defined as weight loss of >5 percent of body weight over the preceding 6 months in the absence of starvation; or body mass index 2 percent; or sarcopenia and weight loss >2 percent. In patients with cancer, cachexia may occur in more than half of all patients with advanced disease. Patients with weight loss prior to initiation of chemotherapy have significantly worse survival in a variety of cancers compared with patients who did not have weight loss prior to chemotherapy.

Assessment: Assessment and selection of a treatment plan for CACS should take a holistic look at the patient and the underlying reasons for their cachexia. First, consider addressing all reversible causes related to appetite loss, including but not limited to nausea, vomiting, dysgeusia, constipation, other metabolic causes (e.g. hyperthyroidism, hypercalcemia). Features which should be evaluated include anorexia or reduced food intake, catabolic drivers (i.e. cancer, sepsis), muscle mass and strength, and effect of cachexia on the patient's quality of life. For assessing appetite loss, clinicians should evaluate and address nausea, early satiety, dysgeusia, constipation and GI tract dysmotility prior to initiation of medications for appetite stimulation.

Considerations: Other co-factors to consider include presence of pain and/or obstructing tumors, altered mood, infections, and food access.

Treatment:

I. General Treatment – Consider referral to a registered dietician for assessment and counseling around practical and safe advice regarding feeding and nutrition. Lack of appetite alone is not sufficient indication for enteral or parenteral nutrition, which have limited efficacy and serious side effects. Consider enteral or parenteral nutrition therapy separately.

- Educate patients and caregivers about CACS and consider treatments in line with their goals of care.
- Consider the addition of one of the medications below if other causes of appetite loss are addressed or are irreversible and CACS persists.

II. Pharmacologic Agents – While many medications may improve some components of CACS, *there is insufficient evidence to routinely recommend any pharmacologic agent* on a regular basis for appetite stimulation. No medications have been FDA approved for appetite stimulation in CACS. ASCO recommends time limited trials of megestrol acetate and dexamethasone only. Any weight gain from these agents is caused by an increase in fat, not lean muscle mass. ASCO recommends against the use of cannabinoids for CACS due to lack of positive evidence. Similarly, mirtazapine is not recommended for CACS.

Generic Drug (Brand)	Starting Dose, Interval, Route	Common Dosage Range	Side Effects	Comments
Megestrol acetate (Megace®)	400 mg PO once daily (40 mg/mL) Use liquid formulation	400-800 mg once daily (40 mg/mL)	**Thromboembolic events**, nausea, diarrhea, edema, adrenal suppression, hyperglycemia, hypertension, sexual dysfunction	- **Caution**: *do not use* in patients at risk of thromboembolic events; higher doses increase risk - Consider minimum 2-week trial; discontinue if no benefit - Taper if prolonged use to avoid adrenal insufficiency - Equally efficacious to dexamethasone as appetite stimulant; associated with fewer long-term side effects - Weight gained appears to be related to water retention or adipose tissue, not lean muscle mass - Superior to dronabinol for appetite stimulation
Table of agents cont'd on next page				

Appetite Stimulation in Cancer-Related Anorexia Cachexia Syndrome (CACS) (cont'd)

Generic Drug (Brand)	Starting Dose, Interval, Route	Common Dosage Range	Side Effects	Comments
Dexamethasone (Decadron®)	2 mg PO once daily	2-8 mg daily in divided doses	Early SE: fluid retention, insomnia, hyperglycemia, mental disturbances Late SE: myopathies, infections	- Efficacious as an appetite stimulant - Many long-term side effects - If given long term (longer than one month) at doses equal to or higher than 4 mg daily, PJP prophylaxis should be considered. Typical PJP prophylaxis regimens include Bactrim DS 1 tablet PO daily or 3 times a week.
Olanzapine (Zyprexa®)	2.5 mg PO once daily	2.5-20 mg daily in 2-3 divided doses	Somnolence, weight gain, QT prolongation, pseudo-parkinsonism	- Can be used as an adjunct to megestrol acetate therapy - Consider EKG monitoring prior to initiation
Dronabinol (Marinol®)	2.5 mg PO twice daily	2.5-10 mg twice daily	Dry mouth, hypotension, somnolence, ataxia, euphoria/dysphoria	- Approved for CINV, may be helpful for nausea as well as appetite stimulation - Early studies in AIDS patients with cachexia showed promising early results; benefits have *not* been demonstrated in the cancer population in an RCT - Side effects are generally mild

References: Appetite Stimulation in CACS list of references can be found on page 22.

Constipation

Susan Mac Isaac, MSN, RN

Description: Constipation is often defined as having fewer than three bowel movements (BM) a week or a decrease in the patient's baseline elimination pattern. Uncomfortable symptoms include hard stools, incomplete emptying, abdominal bloating, discomfort, and excessive straining. Constipation can be one of the most disturbing symptoms experienced by patients with serious illness and occurs in at least 70% of patients with serious or chronic illness. Chronic idiopathic constipation warrants referral to GI specialists.

Assessment: Obtain a subjective report of ease of defecation, feeling of incomplete bowel evacuation, last bowel movement, and general judgement regarding constipation during the last 7 days. A complete physical examination including a rectal examination may be performed if indicated to assess for impaction; avoid rectal exam in patients with low blood counts.

Considerations: Many factors cause or contribute to constipation and can include:

- Lab abnormalities – hypercalcemia, hypokalemia
- Physical factors – peritoneal studding with cancer, bowel obstruction, damage to the spinal cord (cauda equina, peroneal nerve plexus), presence of tumor in or around the rectum, hemorrhoids, anal fissures triggering pain, surgical reduction of rectal capacity, radiation-induced fibrosis of the anorectum.
- Medications – opioids, tricyclic antidepressants, ondansetron, scopolamine, oxybutynin, promethazine, diphenhydramine, lithium, verapamil, bismuth, iron, aluminum, calcium salts, anticholinergics
- Environmental and social factors: inactivity, lack of private space to defecate, poor food or fluid intake, stress, depression, sedation, loss of consciousness, confusion (can affect sensory awareness of the need to defecate).

Treatment:

I. General Treatment –

- Add natural sources of fiber, increase fluids as tolerated.
- Increase mobility and exercise as tolerated.
- Establish regular pattern of bowel movements, timed toilet training, diaphragmatic breathing.
- Integrative therapy options: biofeedback, aromatherapy, massage.
- Consider digital disimpaction as necessary.

II. Pharmacologic Agents – Begin by asking patient what treatment has been effective in the past. All agents should be trialed until maximum dose is reached/ painful complications occur. *Listed order of agents on the table is the general preferred sequence of introduction of agents.*

Generic Drug (Brand)	Starting Dose, Route, Interval	Common Dosage Range	Side Effects	Comments
Senna (Senokot®)	8.6 mg PO once daily	2-4 tabs daily in divided doses MAX 8 tabs per day	Stomach cramping, diarrhea	- Available as a tea - Often combined with docusate sodium in over-the-counter formulations
Polyethylene glycol (MiraLAX®)	17 gm PO in 4 oz fluid	1-2 capfuls daily in divided doses	Stomach discomfort, diarrhea, flatulence	- Individual packets available - May take 2-4 days before BM
Bisacodyl (Dulcolax®)	PO: 5 mg once daily PR: 10 mg once daily	5 to 15 mg daily in divided doses	PO: Abdominal discomfort, diarrhea PR: Proctitis abdominal cramps, diarrhea, nausea, caution low blood counts	- Best taken in the evening before BM is desired - Rectal formulation CI in myelosuppression
Magnesium hydroxide (Phillips'® Milk of Magnesia)	30 mL (400 mg/ 5 mL) PO once daily	30 to 60 mL daily in divided doses	Stomach cramping, diarrhea	- May induce BM quickly (30 min to 6 hrs)

Table of agents cont'd on next page

Constipation (cont'd)

Generic Drug (Brand)	Starting Dose, Route, Interval	Common Dosage Range	Side Effects	Comments
Lactulose (Enulose®)	15 mL PO once daily	15-30 mL daily Max 60 mL per day	Abdominal pain, diarrhea, flatulence	**Do not use in lactulose deficient patients**
Magnesium citrate (Citroma®)	195-300 mL PO in single daily dose or in divided doses with full glass of water	Half to one bottle	Abdominal pain, diarrhea, flatulence, electrolyte imbalance	- Renal failure - May recommend smaller dose (half bottle)
Enema	*See enema table below*			
Docusate sodium (Colace®)	50 mg PO once daily	50 to 300 mg daily in divided doses	Bitter taste, diarrhea, nausea, cramping	Evidence does not support use in Hospice setting; not included in typical regimen

Enemas *(Listed order of enemas on table is the general preferred sequence of enema trial)*			
Enema Type	**Dose**	**Side Effects**	**Comments**
Outpatient Use		Fleet® Saline: Hyperphosphatemia (**CI in patients with renal failure**) All enemas: stomach cramping, diarrhea, flatulence. Caution/ **avoid use** in neutropenia, thrombocytopenia	
Monobasic Sodium Phosphate Monohydrate (Fleet® Saline)	118 mL as a single dose PR		
Bisacodyl (Fleet® Bisacodyl)	30 mL as a single dose PR		
Inpatient Use			
Soap Suds	*Nurse prepared*		May combine with mineral oil
Mineral Oil	118 mL as a single dose PR		If no stool >5 days, use mineral oil enema immediately before soap suds enema
Milk & Molasses	30 mL milk + 30 mL molasses, mixed, as a single dose PR		

III. Special Circumstances –

- Patients with spinal cord injury or tumors may require scheduled PR medications to maintain regular bowel movement.
- If patients are having difficulty passing gas, consider evaluation for bowel obstruction (see page 21).
- For specific treatment of **opioid-induced constipation** (OIC), utilize a prevention/maintenance regimen. Metamucil is not recommended for OIC. Refer to the **Pink Book** for more details.

References: Constipation list of references can be found on page 22.

Delirium

Linda Drury, PA

Description: Delirium is a condition characterized by acute changes in mental status. Mental status may fluctuate throughout the day from appearing normal to periods of agitation, confusion, or hypoactivity. Delirium is often worse at night. Delirium may be reversible unlike dementia, which is progressive and irreversible.
Manifestations may include: Inattentiveness, reduced awareness of the environment, difficulty keeping up conversation, easily distractibility, disorientation, nonsensical speech, word finding difficulty, sleep disturbance, visual/audio hallucinations, restlessness or lethargy, agitation, calling out, moaning, emotional lability, inappropriate behavior, paranoia, anxiety.
There are 3 types of delirium: 1. Hyperactive (agitation, restlessness) 2. Hypoactive (withdrawal, confusion) 3. Mixed Hyperactive and Hypoactive. Severity of delirium may range from mild (disorientation, confusion, mild agitation) to severe (combative, dangerous to self or others).

Assessment: Determine patient's baseline status from family and friends who know the patient. Assess for presence of delirium using a screening tool e.g., Confusion Assessment Method (CAM) (see CAM diagnostic algorithm below).
Assessment for underlying causes may include:

- Vital Signs: assess for fever, hypoxia, pain, urinary retention, constipation
- Medications: review recent medication changes/additions, and medications known to contribute to delirium including those below.
- Labs: assess for leukocytosis, abnormal renal and liver function, UTI (may be asymptomatic), abnormal glucose, sodium, hypercalcemia (corrected for albumin level or ionized calcium), B12 (note: Folate deficiency does **not** cause delirium). If indicated, evaluate further for infection, brain metastasis, and medication withdrawal. Consider urine toxicology screen.

Considerations: Many factors contribute to delirium. It is important to look for etiologies that can be reversed.

- Anatomic reasons: urinary retention, fecal impaction, constipation, brain lesions i.e., stroke, parenchymal lesions, leptomeningeal disease.
- Medications include: benzodiazepines, which can cause a paradoxical reaction; anticholinergics, especially scopolamine; steroid; opioids; acute discontinuation/withdrawal of chronic medications that require tapering (e.g., antidepressants opioids, gabapentin, glucocorticoids, baclofen); antibiotics (cefepime), famotidine (in the elderly), unprescribed medications patient or family may bring in to the hospital.
- Iatrogenic factors: dehydration, sleep deprivation, unrelieved pain.
- Sensory deficits in vision, hearing.
- Life threatening etiologies can include anticholinergic crisis, serotonin syndrome, neuroleptic malignant syndrome (NMS).
- Terminal delirium is unlikely to be reversible.

Treatment:

I. General Treatment –

- Utilize non-pharmacologic interventions to minimize risk of delirium including early mobilization, minimize sleep disruption (no VS overnight), maximize day/night cycle with lights on in the day, soft lighting at night, frequent reorientation, minimize TV and noise.
- Make sure patient has home devices such as dentures, glasses, hearing aids. Have family bring in familiar items from home such as photos, music.
- Allow family/caregivers to remain at bedside if possible.

Delirium (cont'd)

II. Pharmacologic Agents – Consider utilizing agents below for *Hyperactive or Mixed Delirium* (i.e., when symptoms are distressing to patient or potentially dangerous to patient or caregivers). All included agents have the potential to prolong QTc. Replete Mg/Ca/K+ as necessary.

Generic Drug (Brand)	Starting Dose, Interval, Route	Common Dosage Range	Side effects	Comments
Haloperidol (Haldol®)	0.5-1 mg PO/IV/SubQ	0.5-2 mg IV/PO/IM Q6H Max single dose: 10 mg (<65 yo), 2 mg (>65 yo or frail)	Sedation	Goal to relieve distress and prevent dangerous behaviors
Olanzapine (Zyprexa®)	2.5-5 mg PO/IV at bedtime	2.5-5 mg PO Q6H	Sedation	Do not administer IV Zyprexa in close proximity to IV benzodiazepines (cardiorespiratory depression)
Quetiapine (Seroquel®)	12.5 mg PO	25-100 mg PO BID-TID	Sedation	Hypnotic effect at low doses
Chlorpromazine (Thorazine®)	25-50 mg PO/IV	25-100 mg PO daily-TID	Sedation	Most sedating

The Confusion Assessment Method (CAM) Diagnostic Algorithm:

CAM Diagnostic Algorithm
Feature 1: Acute Onset or Fluctuating Course This feature is usually obtained from a family member or nurse and is shown by positive responses to the following questions: Is there evidence of an acute change in mental status from the patient's baseline? Did the (abnormal) behavior fluctuate during the day, that is, tend to come and go, or increase and decrease in severity?
Feature 2: Inattention This feature is shown by a positive response to the following question: Did the patient have difficulty focusing attention, for example, being easily distractible, or having difficulty keeping track of what was being said?
Feature 3: Disorganized thinking This feature is shown by a positive response to the following question: Was the patient's thinking disorganized or incoherent, such as rambling or irrelevant conversation, unclear or illogical flow of ideas, or unpredictable switching from subject to subject?
Feature 4: Altered Level of consciousness This feature is shown by any answer other than "alert" to the following question: Overall, how would you rate this patient's level of consciousness? (alert [normal]), vigilant [hyperalert], lethargic [drowsy, easily aroused], stupor [difficult to arouse], or coma [unarousable]).
The diagnosis of delirium by CAM *requires* the presence of features 1 and 2 and *either* 3 or 4.

References: Delirium list of references can be found on page 23.

Acute, Non-infectious Diarrhea

Molly Bacon, PharmD

Description: Diarrhea is the passage of loose or watery stools, typically at least three times in a 24-hour period. The increased water content of the stool can be caused by impaired water absorption and/or active water secretion by the bowel. Acute diarrhea lasts ≤ 14 days, persistent diarrhea is between 15-30 days, and chronic diarrhea persists for > 30 days. Dysentery or invasive diarrhea contains visible blood or mucous, in contrast to watery diarrhea, and is commonly associated with fever and abdominal pain. This review only covers management of acute, non-infectious diarrhea.

Assessment:
Physical exam: Evaluate total body volume status assessing mucous membranes, skin turgor, blood pressure including postural (orthostatic), and altered sensorium. Evaluation should be completed to rule out ileus, impaction, or peritonitis by looking for abdominal distension, pain with gentle percussion, abdominal rigidity, rebound tenderness, or stool balls in the rectum.
Labs: BMP, checking for hypokalemia or renal dysfunction, blood cultures in those with other signs or symptoms of infection, stool tests for pathogens (see below).

Considerations: Rule out infectious sources of diarrhea, of which major causes include viruses, bacteria (e.g., C. difficile), and protozoa. Both immunotherapy and chemotherapy can cause diarrhea and management may require dose reductions. In the setting of patients with cancer on immunotherapy treatment, colitis must also be considered. Opioid tapering and/or withdrawal can cause diarrhea until withdrawal symptoms have resolved. Carcinoid syndrome (from carcinoid tumors that release serotonin) can also cause diarrhea.

Treatment:

I. General Treatment –
Initial management should begin with fluid repletion, nutrition management, and diet adjustments.

- Fluid repletion – preferably by the oral route if gut is functioning, with solutions that contain water, salt, and sugar. Patients with more severe hypovolemia should initially receive intravenous fluid repletion. Diluted fruit juices and flavored soft drinks along with crackers and broths or soups may meet the fluid and salt needs in patients with mild illness. Oral rehydration solutions, such as Rehydralyte and Ceralyte are appropriate for patients with more severe diarrhea.
- Dietary recommendations – discontinue lactose and caffeine containing products, alcohol, high fat content foods, and high osmolar supplements. Increase fluid intake as tolerated, consume boiled starches (e.g., potatoes, noodles) oats, cereals, crackers, bananas, soup, and boiled vegetables as tolerated.

II. Pharmacologic Agents –
Patients with bothersome symptoms may benefit from pharmacologic therapy. All agents should be discontinued when diarrhea resolves. Since medication management is for non-infectious diarrhea, avoid use in cases of fever. For patients on laxatives (e.g., OIC treatment), discontinue laxatives as the first step when treating diarrhea. *Listed order of agents on the table is the general preferred sequence of introduction of agents.* All medications can be used in combination on an as needed basis, and agents should be maximized as tolerated.

Generic Drug (Brand)	Starting Dose, Route, Interval	Side Effects	Comments
Loperamide (Imodium®)	4 mg PO once, then 2 mg PO Q4H PRN with each loose stool MAX per package insert = 16 mg/day, studies up to 54 mg/day show few adverse effects	Dizziness, constipation, cramping, abdominal pain	Do not use if infectious diarrhea (e.g., C. diff) is suspected
Diphenoxylate and atropine (Lomotil®)	5 mg diphenoxylate PO Q6H PRN until control achieved MAX 20 mg diphenoxylate/day for 2 days or max of 10 days at lower doses	Central opiate and cholinergic side effects; flushing, tachycardia, confusion, headache, fluid retention	- Lower doses can be trialed and effective for control - Discontinue if no improvement after 10 days at max dose
Table of agents cont'd on next page			

Acute, Non-infectious Diarrhea (cont'd)

Generic Drug (Brand)	Starting Dose, Route, Interval	Side Effects	Comments
Bismuth salicylate (Pepto-Bismol®, Kaopectate®)	524 mg tablet or 30 mL every 0.5-1 hour for 8 doses MAX 4192 mg/day for max 2 days	Potential of salicylate toxicity - **avoid in those taking aspirin** and pregnant women	- Can cause dark stools and tongue - Useful in situations where loperamide must be avoided and for symptomatic control against organisms such as E. coli - May take up to 48 hours to produce an effect and can interfere with absorption of certain medications (must space out timing accordingly)
Opium tincture	6 mg (0.6 mL) of undiluted opium tincture (10 mg/mL) 4x daily or 10-15 drops orally in water every 3-4 hours	CNS depression, bradycardia, hypotension, decreased urine output	May be less effective for patients already on opioids

III. Special circumstances –

For all special circumstances and/or refractory diarrhea, refer to primary oncologist and consider GI consult.

- For Colitis, refer to BWH Immunotoxicity (iTOX) team for current management.
  - Consider stool tests including bacterial cultures.
  - Taper steroids as tolerated when diarrhea resolves.
- For pancreatic cancer, consider pancreatic enzyme replacement therapy to address related diarrhea, weight loss, etc.

- For secretory diarrhea/ carcinoid syndrome, see table below for general guidance:

Generic Drug (Brand)	Starting Dose, Route, Interval	Side Effects	Comments
Octreotide (Sandostatin®)	100 mcg SubQ BID-TID initially or continuous infusion at a rate of 10-80 mcg/hr until symptoms resolve MAX 200 mcg SubQ BID-TID	Nausea, headache, dry mouth	SubQ shots painful
Telotristat Ethyl (Xermelo®)	250 mg PO TID	Peripheral edema, headache, depression, nausea, vomiting	Carcinoid syndrome diarrhea inadequately controlled by somatostatin analog (SSA) therapy
Note: These special circumstances need to be treated with primary services and are outside the scope of the Orange Book.			

References: Diarrhea list of references can be found on page 23.

Dyspnea

Jason Bowman, MD

Description: Dyspnea is a subjective experience of breathing discomfort that consists of various qualitatively distinct sensations. Most palliative care patients will experience dyspnea during their illness, particularly those with advanced cancer, heart failure, and/or chronic lung disease. Dyspnea has been shown to worsen quality of life and is strongly linked to other symptoms such as anxiety. Dyspnea also adversely affects family members, caregivers, and healthcare providers. Tachypnea is distinct from dyspnea and does not have the same implications for assessment or treatment.

Assessment: Similar to pain assessment, the mainstay of dyspnea assessment is patient self-report. No exam finding, or laboratory/radiographic test can indicate the presence of dyspnea or its severity. In verbal patients, numerous validated scoring tools can be used in a regular ongoing manner, such as the Baseline Dyspnea Index, (BDI). The Respiratory Distress Observation Scale (RDOS) is the only validated tool for assessment of dyspnea in non-verbal patients.

Considerations: Evaluate the patient for primary pulmonary, cardiac (e.g., fluid overload), metabolic, and hematologic causes with appropriate tests. Also consider underlying causes of anxiety, delirium, and other psychosocial or spiritual distress. It has been postulated that endogenous opioids (aka "endorphins") likely attenuate the sensation of dyspnea.

Treatment: Provide symptomatic treatment while attempting to identify and treat the underlying cause of dyspnea, collaborating with specialists as appropriate. Symptomatic treatment includes pharmacologic and other interventions.

I. General Treatment –

- Use of fans to blow air onto patients with dyspnea has been common practice for decades. The mechanism of benefit is theorized to be stimulation of thermal and mechanical receptors in patients' trigeminal nerves (within the cheek and nasopharynx).
- Pulmonary rehabilitation with a structured program delivered by trained specialists has strongly been shown to be effective. Literature shows moderate evidence of improvement of exertional dyspnea when walking aids and similar energy conservation strategies were used.
- There is no clear data to support the use of supplemental oxygen in general for patients who are not hypoxemic, though patients may find it gives them comfort (e.g., non-hypoxemic COPD patients during exercise.)
- Psycho-social-spiritual support, relaxation techniques, and acupuncture have mixed results in effectiveness and anecdotally may be helpful in some patients.

II. Pharmacologic Agents –

- Short-acting opioids are the first line treatment for dyspnea via oral or parenteral routes. Morphine, hydromorphone, oxycodone, and fentanyl are **equally effective**. For opioid naïve patients, opioids can be helpful for dyspnea at lower doses (typically half) than those required for treatment of pain. If your patient is already taking opioids for pain, use the rescue dose as the initial dose for dyspnea. Low doses of opioids have not been shown to increase overall risk of respiratory depression, hospitalization, or death. Extra caution should be used with patients who have sleep apnea and/or concurrent benzodiazepine use.

Generic Drug (Brand)	Starting Dose, Interval, Route	Side Effects	Comments
Morphine	IV: 2-5 mg Q2H PRN PO liquid (10 mg/ 5 mL): 5-10 mg Q3-4H PRN PO tab: 7.5-15 mg Q3-4H PRN	Sedation, nausea, constipation	**Morphine & oxycodone:** avoid use in patients with poor renal function **All:** - Extra caution when used with sleep apnea patients - Continuous infusion or long-acting opioids or transdermal patches are not indicated for initial therapy of dyspnea. - If on oral opioids for pain, the same opioid can be used first-line for dyspnea
Hydromorphone	IV: 0.5-1 mg Q2H PRN PO: 2-4 mg Q3-4H prn Q		
Fentanyl	10-25 mcg IV Q1-2H PRN		
Oxycodone	2.5-5 mg PO Q3-4H PRN		

- Benzodiazepines are useful for anxiety-related dyspnea but can lead to delirium and respiratory depression with opioid use.
- Data about inhaled pharmacologic options such as furosemide, saline and inhaled opioids are conflicting, ineffective, or limited.
- Other psychiatric medications such as antidepressants have not been clearly shown to have benefit.
- Methadone should not be used for dyspnea.

References: Dyspnea list of references can be found on page 23.

Cancer-Related Fatigue

Sarah Given, DNP, ANP-BC

Description: Cancer-related fatigue (CRF) is a subjective symptom described as physical, emotional, or cognitive exhaustion that is not proportional to activity level. The exhaustion is severe enough that it impacts function and is not relieved by rest. It is estimated that 50-90% of patients experience cancer-related fatigue (CRF) at some point in their disease trajectory and it can occur throughout most modalities of cancer treatment, including treatment with chemotherapy, radiation, bone marrow transplant, and biologic agents. It is also common in cancer survivors. The exact mechanism of cancer-related fatigue is unknown.

Assessment: Screening for the presence of fatigue should take place at initial appointment and at regular intervals. Because fatigue is subjective, use of patient self-reporting tools such as eSyM at DFCI (electronic Symptom Management program recorded in EPIC), can be helpful to screen for fatigue. A brief, quantitative measure, such as Patient Reported Outcome Measures PROMs (available at DFCI) can also be used. Edmonton Symptom Assessment System (ESAS) is a multi-symptom screening tool in which patients rate their symptoms on a scale of 0-10. Tools that specifically screen for fatigue include the BFI (e.g., Brief Fatigue Inventory), used for patients who report moderate to severe fatigue.
An evaluation of fatigue should include cancer history (disease status and treatment history), labs, review of medications, detailed fatigue history, a physical exam, and nutritional evaluation. The evaluation should be focused on identifying any treatable/reversible factors that may contribute to fatigue.

Considerations: The etiology of CRF is multidimensional. Possible contributing factors to consider may include:

1. Tumor related factors and complications such as electrolyte abnormalities, anemia, cachexia, PE, fever
2. Comorbid conditions such as heart failure, COPD, infection
3. Iatrogenic factors such as chemotherapy, radiation
4. Physical symptoms such as pain, anorexia
5. Medications such as opioids, antiemetics, psychiatric medications
6. Behavioral factors such as anxiety, depression, poor sleep, decreased physical activity

Treatment: Treatment should first focus on treating underlying causes of fatigue (electrolyte imbalances, hypothyroid, etc.). Depending on disease status, it may be appropriate to pause cancer directed therapy. All patients should receive education about fatigue and should be taught general management strategies.

I. General Treatment –

- Physical activity: Optimal physical activity has the strongest evidence for treatment of **treatment-related** fatigue and should be based on an individual's overall health status. This can include walking, yoga, exercises of varying intensity levels. **Caution** in patients with bone metastases, thrombocytopenia, coagulation disorders, anemia, fevers, risk of falls. In those circumstances, consider referral to PT, OT, functional medicine.
- Other modalities that can play a significant role include bright white light therapy, sleep interventions such as CBT-i (see Insomnia page 16-17), and energy conservation (set realistic activity goals, pace/schedule activities, utilize labor saving devices, delegate tasks). Psychosocial interventions such as cognitive behavioral therapy (CBT), mindfulness, psycho-educational therapy can also be of benefit. DFCI resources are available at the Zakim Center for Integrative Therapies and Healthy Living (contact at 617-632-3322, no patient referral needed).

II. Pharmacologic Agents –

There is limited evidence to support the use of pharmacologic intervention in the treatment of fatigue. However, it may be appropriate to consider these agents if fatigue persists.

Generic Drug (Brand)	Starting Dose, Route, Interval	Common Dosage Range	Side Effects	Comments
Methylphenidate (Ritalin®) *ER formulations are available and may be used in certain situations*	5 mg PO 1-2x/ day as needed MAX: 40 mg daily	Can increase up to 40mg/day in divided dose	Insomnia, irritability, anorexia	- Second dose before 2 pm to avoid impact on sleep. - Cautions: CVD events, psychiatric illness, older adults may need lower start dose.
Dexamethasone (Decadron®)	2 mg PO QAM	2-4 mg BID	Short-term: insomnia, high glucose, weight gain Long-term: immunosuppression, moon face, osteoporosis	- Discuss with oncology team prior to initiation of steroids due to possible interaction with treatment. - BID dosing no later than 2 pm to decrease impact with night sleep.

Additional agents found in literature on CRF include modafinil (Provigil), bupropion (Wellbutrin), and megestrol acetate (Megace). Due to poor quality/ volume of evidence, these agents are generally not recommended.

References: Cancer-Related Fatigue list of references can be found on page 24.

Insomnia

Victor Phantumvanit, PharmD

Description: Insomnia is a sleep disorder characterized by difficulty falling asleep, frequent nighttime awakenings, and/or difficulty staying asleep. It is associated with daytime symptoms including impairment in cognitive performance, fatigue, daytime sleepiness, and mood disturbances. It is more commonly seen in older adults, medically ill, and patients with psychiatric illness. It is considered chronic when it occurs at least three times per week and persists for at least 3 months.

Assessment: Three criteria must be met for a diagnosis of insomnia: 1. adequate opportunity for sleep, 2. symptoms of trouble falling or staying asleep, and 3. daytime dysfunction.

Considerations: When treating insomnia, treatment of the underlying etiology should be considered first. Considerations include insomnia due to treatment-related anxiety, delirium, psychiatric disorders, pain, urinary disturbances, medication doses, or rapid cessation of some medications such as corticosteroids or SSRIs. There are other sleep disorders that can present with symptoms of insomnia such as restless leg syndrome and obstructive sleep apnea. Other causes of sleep disturbances, such as inadequate opportunity to sleep or any environmental circumstances should be initially addressed. If patients are receiving medications for mood disorder that cause sedation, consider bedtime dosing. Do not time steroids or other activating medications (e.g., methylphenidate) near bedtime.

Treatment:

I. General Treatment –

- Practicing healthy sleep habits: no electronics 30-60 minutes before bed, decreasing large meals before bed, only using the bed for sleep-related activities, decreasing caffeine intake in the afternoon and evening, decreasing alcohol consumption.
- Caution against use of medications with active ingredient diphenhydramine (e.g., Benadryl/Tylenol PM).
- CBT-i (Cognitive Behavioral Therapy for insomnia) is the preferred management. If not feasible or ineffective alone, consider adding medication management. If insomnia persists despite CBT-i and medication management, consider referral to outpatient sleep specialist.

II. Pharmacologic Agents – It is recommended to first trial CBT-i. Clinicians may consider dual therapy role for medications already on patient's list, such as SSRIs. Z-drugs (non-benzodiazepine sedatives such as zaleplon, zolpidem, and eszopiclone) initiated for insomnia should only be used **short-term**. Benzodiazepines are not indicated for insomnia. Trazodone has anecdotal evidence for insomnia.

To improve sleep onset (desired effect not seen until 1 hour; should not be used PRN):

Generic Drug (Brand)	Starting Dose, Interval, Route	Side Effects	Comments
Melatonin	3-5 mg PO in the evening 1-2 mg PO 1 hour before bedtime in older patients Max: 10 mg PO in the evening	Headache, transient depression, dizziness, nausea, irritability	- Natural product - Many formulations available
Ramelteon (Rozerem®)	8 mg PO within 30 minutes of bedtime Max: 8 mg PO daily	Dizziness, somnolence, fatigue, nausea, higher doses (>30 mg) may cause insomnia	- Increased exposure: CYP1A2, CYP3A4, & CYP2C9 inhibitors - Decreased exposure: CYP3A4 inducers
Zaleplon (Sonata®)	10 mg PO immediately before bedtime 5 mg PO in lower weight individuals Max: 20 mg PO daily	Complex sleep behaviors including sleep walking, sleep driving, and engaging in other activities while not fully awake (**BBW**), headache, dizziness, drowsiness	- Additive effects with CNS depressants

Table of agents cont'd on next page

Insomnia (cont'd)

Generic Drug (Brand)	Starting Dose, Interval, Route	Side Effects	Comments
Zolpidem (Ambien®)	ER tablet: 6.25 mg PO (females) or 6.25-12.5 mg PO (males) immediately before bedtime Max: 12.5 mg PO once daily IR tablet, spray, or sublingual tablet: 5 mg PO (females) or 5-10 mg PO (males) immediately before bedtime. Max: 10 mg PO once daily	Complex sleep behaviors including sleep walking, sleep driving, and engaging in other activities while not fully awake (Black Box Warning), headache, drowsiness, dizziness, diarrhea, effect on short-term memory	Drug interactions: - Use with CNS depressants leads to additive effects - Use with imipramine & chlorpromazine leads to impaired alertness and psychomotor performance - Increased exposure: CYP3A4 inhibitors - Decreased exposure: CYP3A4 inducers

To improve both sleep onset and sleep maintenance:

Generic Drug (Brand)	Starting Dose, Interval, Route	Side effects	Comments
Suvorexant (Belsomra®)	10 mg PO once daily within 30 minutes of bedtime Max: 20 mg PO once daily	Headache, dizziness, abnormal dreams, xerostomia	Contraindicated in patients with narcolepsy
Eszopiclone (Lunesta®)	1 mg PO immediately before bedtime Max: 3 mg PO daily	Complex sleep behaviors including sleep walking, sleep driving, engaging in other activities while not fully awake (**BBW**), drowsiness, dizziness, headache, dysgeusia	- Additive effects with CNS depressants - Caution with CYP3A4 inhibitors

References: Insomnia list of references can be found on page 24.

Oral Mucositis

Linda Drury, PA, Molly Bacon, PharmD

Description: Mucositis is defined as the painful breakdown of mucosal membranes from a variety of factors. The pain is different from other pain syndromes in that it can be acute and incidental. Mucositis causes exquisite pain that can occur with minimal movement of the mouth and tongue, such as talking and swallowing (even swallowing one's own secretions).

Assessment: Assess ability to eat, drink, take oral medications, maintain hydration. Mucositis with painful swallowing below the throat may indicate that the esophagus is also affected (esophagitis). Consider including an overall quality of life assessment. Assess for concurrent viral, bacterial, or fungal infections.

Considerations: Causes include anticancer therapy and radiation therapy. Risk factors include pre-disposing medications (e.g., broad-spectrum antibiotics, steroids), external beam radiation, and neutropenia, and allergies to medications (e.g., ACE inhibitors). The pain and discomfort from mucositis can be aggravated by oral infections such as HSV and candida.

- Chemotherapy agents with high risk for mucositis include 5-fluorouracil (5-FU), doxorubicin, and methotrexate. Mucositis from other chemotherapy agents may be more dose dependent. Mucositis can occur several days after chemotherapy treatment, and usually improves with WBC recovery.
- Radiation-induced mucositis in head and neck cancer patients usually occurs 2-3 weeks into a course of treatment and can last for many weeks following completion of radiation.

Treatment:

I. General Prevention and Treatment –

Prevention tactics may reduce severity of symptoms.

- Good oral hygiene includes daily brushing with a soft toothbrush, flossing, and mouth rinses to remove bacterial overgrowth, such as povidone iodine, chlorhexidine, or a mixture of baking soda, salt, and water. Cryotherapy (ice chips) can be used with the administration of anticancer agents at high-risk of inducing mucositis.
- Chemotherapy and/or radiation therapies may need to be adjusted, including dose, frequency, and overall treatment duration. Dentures may not be well tolerated during periods of acute mucositis.
- Palifermin can be used for patients with head & neck cancer or undergoing stem cell transplant (SCC).
- Low frequency laser therapies may be used in select patients with head & neck cancer.

Treatment includes utilizing alcohol-free rinses like povidone iodine, chlorhexidine, saline, and sodium bicarbonate (avoid mouth rinses with alcohol). Diet should include soft, moist foods. Avoid very hot, very cold, spicy, acidic, salty foods. Avoid tobacco and alcohol. Topical honey may be soothing. Thrush can be treated with antifungal agents (consider a longer course if esophagitis is suspected). HSV infection can be treated with antiviral therapy. M-TOR inhibitor induced mucositis can be treated with steroid mouthwash. Consult with Radiation Oncology regarding radiation-specific mouthwash treatments (e.g., steroid rinses). Refractory cases may also warrant Oral Medicine consultation.

II. Pharmacologic Agents –

For severe mucositis, topical agents will likely not be adequate for pain control. Consider rapid-acting treatments for severe acute pain, including opioids administered via IV (e.g., PCA) and/or orally dissolving formulations. For general Patient-Controlled Analgesia (PCA) guidance, refer to the **Pink Book**. Mucositis may require shorter bolus intervals for adequate pain management. Note: "Swallow" route of agents is useful for esophagitis.

Generic Drug (Brand)	Starting Dose, Interval, Route	Common Dosage Range	Side Effects	Comments
2% Viscous lidocaine (Xylocaine®)	10 mL topical swish and spit Q3H PO PRN	10-30 mL; start with 10 mL	Numbing, difficulty protecting airway	Monitor swallowing food/liquids for 60 minutes after use
"Magic Mouthwash" (MBX): Maalox, Benadryl, Xylocaine 1:1:1	10 mL topical swish and spit or swallow Q3H PO PRN	10-30 mL; start with 10 mL	Taste changes, numbness, if swallowed drowsiness, nausea	Formulations may vary

Table of agents cont'd on next page

Oral Mucositis (cont'd)

Generic Drug (Brand)	Starting Dose, Interval, Route	Common Dosage Range	Side Effects	Comments
Sucralfate suspension (Carafate®)	1 gm topical swish and spit or swallow QID PRN	1 gm po QID	N/V, diarrhea, constipation	If swallowed routinely, may interfere with absorption of other medications
0.2% Morphine mouthwash	Topical, hold 10 mL in mouth for 2 minutes then spit out Q3H PRN	10-15 mL	Avoid swallowing due to systemic side effects	Morphine mouthwash is most useful for oral pain instead of esophageal since it is not swallowed
Opioids IV/PO/PG/transdermal (morphine, hydromorphone, fentanyl, buprenorphine) **See Pink Book**	IV: nurse boluses or a PCA with lower doses as frequently as Q10 minutes	*Dosing depends on patient's opioid history and tolerance.* *The appropriate dose and timing should reduce pain without causing sedation, confusion, or respiratory depression.*	Constipation, nausea, sedation, confusion, respiratory depression Opioid solutions may cause oral discomfort when taken PO	Consider a long-acting opioid formulation along with breakthrough agent if mucositis is expected to persist or worsen
Note: Buccal opioid formulations are fast-acting; however, they are difficult to obtain, and prescriptions require REMS certification. If continuing use of buccal opioid after discharge from hospital, appropriate outpatient provider must be identified. It is important to note that buccal formulations are NOT interchangeable – must start with lowest dose if switching formulations.				

References: Oral Mucositis list of references can be found on page 24.

Respiratory Secretions

Iman Suliman, PharmD

Description: Respiratory secretions can be bothersome to patients with pulmonary diseases (e.g., lung cancer patients during radiation treatment) due to excessive mucus production, poor cough response, or ineffective mucociliary clearance. In addition, terminal respiratory secretions result when patients lose their ability to clear secretions in the dying process, which produces rattling-like noises. This has been previously referred to as the "death rattle"; however, this language should be avoided. Education can be provided to family and caregivers that terminal secretions are expected, common, and are not believed to cause respiratory distress.

Assessment: Assess quantity and quality of secretions (thick vs. thin) and consider providing immediate relief through suctioning if applicable. Assess the etiology of secretions. Oral hypersecretions that are thin respond best to pharmacological measures. Bronchial and alveolar secretions do not respond to these agents. For terminal secretions, continue assessing patient every 4 hours in the last days of life to detect and adjust treatment to bothersome symptoms and/or side effects.

Considerations: Rule out the presence of bacterial respiratory infections requiring antibiotics. The goals of intervening include promoting expectoration, increasing mucociliary clearance and conduction of the secretions to the upper airways, and/or improving cough effectiveness. Medications may worsen thick secretions and cause mucus plugging.

For terminal secretions, pharmacological agents have not been shown to be more effective than placebo, and no agent has demonstrated superior efficacy. However, glycopyrrolate does not cross the blood brain barrier (BBB); thus, may cause less delirium and sedation than other anti-secretory medications. Doses should be titrated slowly to patient response. Minimize IV therapy, including hydration, as consistent with goals of care.

Treatment:

I. General Treatment – Gentle suctioning, repositioning patient in the lateral recumbent position, postural drainage, nebulized hypertonic saline (3%).

II. Pharmacologic Agents –

Generic Drug (Brand)	Starting Dose, Route, Interval	Side Effects	Comments
Glycopyrrolate (Robinul®)	0.2 – 0.4 mg subQ, IV Q2-4H PRN MAX: 2.4 mg IV per 24 hours	Blurred vision, palpitations, constipation, urinary retention, dry mouth (over drying can cause thick mucus; moisten mouth periodically)	Quaternary amine (does not cross BBB), poor oral absorption
Hyoscyamine hydrobromide (Levsin®)	0.125 – 0.25 mg SL Q4H	All anti-cholinergic drugs that can cause: Blurred vision, sedation, delirium, restlessness, hallucinations, palpitations, constipation, urinary retention, dry mouth (over drying can cause thick mucus; moisten mouth periodically)	
Atropine sulfate (Atreza®)	0.4 mg subQ, IV Q4-6H		
Scopolamine hydrobromide (Transderm-Scop®)	1.5 mg transdermal patch Q72H		
Guaifenesin (Mucinex®, Robitussin®)	200-400 mg PO Q6H	N/V	Stimulates cough reflex, loosens and thins secretions Caution with use: may increase secretions and worsen cough Avoid use in terminal secretions

References: Respiratory Secretions list of references can be found on page 24.

Malignant Small Bowel Obstruction

Victor Phantumvanit, PharmD

Description: Small bowel obstruction (SBO) is a mechanical or functional obstruction of the small intestine that prevents digestion and forward flow of gastric and intestinal contents. This is commonly seen in patients with abdominal or pelvic cancers, and is most prevalent in ovarian, colorectal, and gastric cancers due to tumors. Presenting symptoms can include colicky pain, abdominal distension, nausea, vomiting, and constipation.

Assessment: Imaging is an important part of SBO assessment. KUB may show air-fluid levels, and distended loops of bowel. CT of the abdomen and pelvis with PO and IV contrast can determine if obstruction is complete/high-grade (transition point seen) or partial obstruction (no transition point).

Considerations: There are other non-malignant etiologies that can cause bowel obstruction including adhesions from prior abdominal surgeries, intra-abdominal infections, and ileus from medications.

Treatment:

I. General Treatment – Place patient on NPO. Change necessary oral medications from home to IV formulation. If extensive vomiting or severe nausea, consider placement of NG tube for decompression. Consider surgical and GI consultation for additional interventions. If refractory, consider palliative care consult.

II. Pharmacologic Agents –

Generic Drug (Brand)	Starting Dose, Interval, Route	Side Effects	Comments
Acute Management of SBO:			
Dexamethasone (Decadron®)	4-8 mg/day IV/PO	Anxiety, insomnia, hyperglycemia	To decrease gut inflammation, GI secretions, and nausea Avoid dosing past 3 pm Consider PPI/H2 blocker
Metoclopramide (Reglan®)	5-10 mg IV/PO every 6 hours standing or PRN	Drowsiness, fatigue, extrapyramidal symptoms (EPS) (caution with other dopaminergic agents)	**DO NOT USE in complete obstruction** Promotes gut motility in **partial obstruction**, decreases N/V Stop if cramping/abdominal pain is worse
Octreotide (Sandostatin®)	100-200 mcg SC BID-TID or 10-25 mcg/hr IV continuous infusion	Hyperglycemia, Hypertension, peripheral edema, sinus bradycardia	Decreases gastric secretions For chronic SBO, initiate LAR octreotide depot 20-30 mg deep IM monthly 2 weeks prior to discontinuation of short-acting
Management of SBO-Induced Nausea/Vomiting and Cramping:			
Antiemetics (choose one):			
Haloperidol (Haldol®)	0.5-1 mg IV/PO every 6 hours, standing or PRN	EPS, Parkinsonism	
Olanzapine (Zyprexa®)	2.5-5 mg IV Q6H PRN	Sedation, weight gain, EPS, Parkinsonism	
Anticholinergics (choose one):			
Glycopyrrolate (Robinul®)	0.2-0.4 mg IV Q6H PRN	Dry mouth	
Scopolamine (Scopace®)	20 mg once followed by 60 mg over 24 hours as continuous subQ, or Patch	Drowsiness, dizziness, Xerostomia, dry eyes, delirium (crosses the BBB)	Decreases gastric secretions/cramping, nausea, and vomiting

References: Malignant Small Bowel Obstruction list of references can be found on page 25.

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