PALLIATIVE CARE NETWORK OF WISCONSIN

Fast Facts Core Curriculum

Non-Pain Symptoms

PALLIATIVE CARE NETWORK OF WISCONSIN

FAST FACTS AND CONCEPTS #1
DIAGNOSIS AND TREATMENT OF TERMINAL DELIRIUM

David E Weissman MD and Drew A Rosielle MD

Background Some degree of loss of cognitive function occurs in most patients in the week or two before death. The typical scenario presented to housestaff is a late-night call from a ward nurse saying, "*Mr. Jones is confused, what should we do*?" This *Fast Fact* reviews assessment and management issues in terminal delirium. See *Fast Fact* #60 for a discussion of newer pharmacological treatments.

Key teaching points:

1. The term "confusion" is not an accurate descriptive term—it can mean anything from delirium, dementia, psychosis, obtundation, etc. Patients need a focused assessment, including a brief mini-mental examination. Clinicians should use one of several validated delirium assessment tools to help quantify and document cognitive function.
2. "Terminal delirium" is not a distinct diagnosis, although it is a commonly used phrase. It implies delirium in a patient in the final days/weeks of life, where treatment of the underlying cause is impossible, impractical, or not consistent with the goals of care.
3. Delirium can be either a *hyperactive /agitated delirium* or a *hypoactive delirium*. The hallmark of delirium is an acute change in the level of arousal; supporting features include altered sleep/wake cycle, mumbling speech, disturbance of memory and attention, and perceptual disturbances with delusions and hallucinations.
4. The most common identifiable cause of delirium in the hospital setting is drugs: anti-cholinergics (e.g. anti-secretion drugs, anti-emetics, anti-histamines, tricyclic anti-depressants, etc.), sedative-hypnotics (e.g. benzodiazepines), and opioids. Other common causes include metabolic derangements (elevated sodium or calcium, low glucose or oxygen); infections; CNS pathology; or drug/alcohol withdrawal.
5. The degree of work-up to seek the cause of delirium is determined by understanding the disease trajectory and overall *goals of care* (see *Fast Fact* #65).
6. The drug of choice for most patients is a neuroleptic. There is one controlled clinical trial of haloperidol versus lorazepam in HIV patients; haloperidol was the superior agent.

Haloperidol is administered in a dose escalation process similar to treating pain. Start haloperidol 0.5-2 mg PO or IV q1hour PRN. Atypical antipsychotics have also been studied for delirium are probably as efficacious as haloperidol. There are insufficient data to make a strong recommendation about the best drug or dosing of antipsychotics for delirium.

7. It is best to think of benzodiazepines as *sedatives* and *anxiolytics* but not as therapy for underlying delirium. On the rare occasion one wants to actually *sedate* a delirious patient a benzodiazepine may be indicated. If anxiety is a prominent part of a patient's delirium, a benzodiazepine may help. Generally, however, benzodiazepines should be avoided as they can cause paradoxical worsening of the delirium and agitation.
8. Non-pharmacological treatments should always be used in delirium management: reduce or increase the sensory stimulation in the environment as needed; ask relatives/friends to stay by the patient; frequent reminders of time/place.

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PALLIATIVE CARE NETWORK OF WISCONSIN

FAST FACTS AND CONCEPTS #5
THE CAUSES OF NAUSEA AND VOMITING (V.O.M.I.T.)

James Hallenbeck MD

Background By understanding the pathophysiology of nausea and targeting antiemetics to specific receptors, therapy can be optimized and side effects minimized. An easy way to remember the causes of vomiting is the **VOMIT** acronym. In the table below receptors involved in different types of nausea are highlighted using this acronym. Blockade of these receptors allows rational, focused therapy.

Cause - Vestibular
- Receptors Involved - Cholinergic, Histaminic
- Drug Class Useful - Anticholinergic, Antihistaminic
- Drug Examples - Scopolamine patch, Promethazine

Cause - Obstruction of Bowel by Constipation (See FF #294 and #295)
- Receptors Involved - Cholinergic, Histaminic, likely 5HT3
- Drug Class Useful - Stimulate myenteric plexus
- Drug Examples - Senna products

Cause - Dys**M**otility of upper gut
- Receptors Involved - Cholinergic, Histaminic, 5HT3, 5HT4
- Drug Class Useful - Prokinetics which stimulate 5HT4 receptors
- Drug Examples - Metoclopramide

Cause - Infection, **I**nflammation
- Receptors Involved - Cholinergic, Histaminic, 5HT3, Neurokinin 1
- Drug Class Useful - Anticholinergic, Antihistaminic, 5HT3 antagonists, Neurokinin 1 antagonists
- Drug Examples – Promethazine (e.g. for labyrinthitis), Prochlorperazine

Cause - Toxins stimulating the chemoreceptor trigger-zone in the brain such as opioids (see FF 25) or chemotherapy (see FF #285)
- Receptors Involved - Dopamine 2, 5HT3
- Drug Class Useful - Antidopaminergic, 5HT3 Antagonists
- Drug Examples - Prochlorperazine, Haloperidol, Ondansetron

Notes
- 5HT3, 5HT4 refer to the serotonin receptors, subtypes 3 & 4.
- Promethazine and prochlorperazine are very different drugs. Promethazine is most useful for vertigo and gastroenteritis due to infections and inflammation. Prochlorperazine is preferred for opioid related nausea.
- There is no evidence supporting the use of lorazepam as a sole agent for nausea. Sedated patients are more prone to aspiration.
- 'O' here relates to 'obstruction' of bowels *by constipation*, not mechanical blockage (see *Fast Facts* #45, 119 for management of mechanical obstructions).
- See FF #93 & #279 for information on cannibinoids and cannabis for nausea and vomiting

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PALLIATIVE CARE NETWORK OF WISCONSIN

FAST FACTS AND CONCEPTS #15
CONSTIPATION

James Hallenbeck MD

Constipation – it's not fun to have or to treat. As with other symptoms, rational therapy should be based on a sound understanding of underlying physiology. Our goal in treating constipation is generally not to "cure" something, but to help the patient return to the best possible balance that will allow a normal bowel movement to be passed. Four major components affect the production of a normal BM: solid waste, water, motility and lubrication.

Solid Waste – Too much or too little is a problem. The intestine is most efficient pushing intermediate volumes. Patients on fiber-poor diets may improve if fiber is added. **Note**: In patients on opioids or patients with minimal fluid intake or poor gut motility (e.g. the dying patient) additional fiber can worsen the situation, causing a 'soft impaction'.

Water Content – Stool water content depends on how much water we drink, our general hydration status, how much water is absorbed from and secreted into the intestine and how fast stool moves through the bowel. Any of these variables can be manipulated. It is easiest to limit absorption (and increase secretion into the gut) by adding osmotically active particles that retain water (e.g. Magnesium salts, non-absorbable sugars such as sorbitol and lactulose, or polyethylene glycol [PEG]). Note: Magnesium and phosphorus salts are contraindicated in renal failure. Hyperosmolar solutions may worsen dehydration by drawing body water into the gut lumen. Sickly-sweet sorbitol and lactulose may be difficult to for patients to tolerate. PEG is flavorless and may be better tolerated.

Motility – Patients with low-activity levels (bed-ridden, dying patients and patients with advanced neurodegenerative disorders) and use of certain drugs (see below) lead to motility problems. Senna preparations, which stimulate the myenteric plexus are generally favored. Use senna tablets (or granules, liquid, or tea), starting with 1 tab QHS, may be gradually increased to 4 tabs BID if needed. Before increasing motility, evacuate existing constipated stool with an enema or cramping can result.

Lubrication simply eases passage and minimizes pain that can interfere with excretion. Most commonly used is dioctyl sodium sulfosuccinate (DSS, or docusate), which decreases stool surface tension much like soap. Usual dosage is 240 mg PO daily or BID. DSS also tastes like soap, so liquid DSS should never be given PO, but may be given to tube-fed patients. Note: DSS is commonly used in combination with senna in opioid-induced constipation, but is generally inadequate as a sole agent. Mineral oil can be used as an enema but should not be given PO, as pneumonitis can result if aspirated. Glycerin suppositories can provide lubrication and draw-in water due to osmotically active particles.

Medications that can cause/exacerbate constipation: Opioids, anticholinergics (tricyclic antidepressants, scopolamine, oxybutinin, promethazine, diphenhydramine), lithium, verapamil, bismuth, iron, aluminum, aalcium salts. See *Fast Facts* #294 and #295 for more information on opioid induced constipation.

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PALLIATIVE CARE NETWORK OF WISCONSIN

FAST FACTS AND CONCEPTS #27
DYSPNEA AT END-OF-LIFE

David E Weissman MD

Introduction Dyspnea is defined as a subjective sensation of difficulty breathing. This *Fast Fact* reviews key elements in the assessment and treatment of dyspnea near the end-of-life.

Etiology The causes of dyspnea include a wide spectrum of serious lung or heart conditions, anemia, anxiety, chest wall pathology, electrolyte disturbances or even urinary retention or constipation.

Assessment Looking for simple problems is always warranted: is the Oxygen turned on? Is the tubing kinked? Is there fluid overload from IV fluids or TPN? Is dyspnea part of an acute anxiety episode, severe pain, constipation or urinary retention? Is there a new pneumothorax or worsening pleural effusion? Understanding 1) where patients are at in the dying trajectory, and 2) their identified goals of care, is essential to guide the extent of workup to discover reversible causes. If the patient is clearly dying (see *Fast Fact* #3), and the goals of care are comfort, then pulse oximetry, arterial blood gases, EKG, or imaging are not indicated.

Treatment

- **General measures** Positioning (sitting up), increasing air movement via a fan or open window, and use of bedside relaxation techniques are all helpful. In the imminently dying patient, discontinuing parenteral fluids is appropriate.

- **Treatment with opioids** Opioids are the drugs of choice for dyspnea at the end-of-life as well as dyspnea refractory to the treatment of the underlying cause. In the opioid naïve patient, low doses of oral (5-10 mg) or parenteral morphine (2-4 mg) will provide relief for most patients; higher doses will be needed for patients on chronic opioids. When dyspnea is acute and severe, parenteral is the route of choice: 1-3 mg IV every 1-2 hours, or more aggressively if needed, until relief in the opioid naïve patient. In the inpatient setting, a continuous opioid infusion, with a PCA dose that patients, nurses or families can administer, will provide the timeliest relief (see *Fast Facts* #28, 54). Nebulized morphine has been reported to provide benefit in uncontrolled case reports, however a controlled trial demonstrated no greater efficacy or lower rate of side effects compared to subcutaneous morphine.

- **Treatment with oxygen** Oxygen is often, but not universally, helpful. When in doubt, a therapeutic trial, based on symptom relief, not pulse oximetry, is indicated in dying patients. A well-designed randomized, controlled trial of oxygen vs ambient air, delivered by nasal cannula, in normoxic patients with advanced illness and dyspnea showed no benefit of oxygen over ambient air delivered by nasal cannula. Patients generally prefer nasal cannula administration than a mask, especially in setting of imminent death when agitation from the mask is commonly seen. There is little reason to go beyond 4-6 L/min of oxygen via nasal cannula in the actively dying patient. Request a face-tent for patients who are claustrophobic from a mask.

- **Treatment with other drugs** Anti-tussives can help with cough (see *Fast Fact* #200), anit-cholinergics (e.g. scopolamine) will help reduce secretions, anxiolytics (e.g. lorazepam) can reduce the anxiety component of dyspnea. Other agents that may have specific disease modifying effects include diuretics, bronchodilators, and corticosteroids.

Family/Team Discussions While there is no evidence that proper symptom management for terminal dyspnea hastens death, the course and management of terminal dyspnea, especially when opioids are used, should be fully discussed with family members, nurses and others

participating in care to avoid confusion about symptom relief vs. fears of euthanasia or assisted suicide (see *Fast Fact* #8).

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PALLIATIVE CARE NETWORK OF WISCONSIN

FAST FACTS AND CONCEPTS #60
PHARMACOLOGIC MANAGEMENT OF DELIRIUM: UPDATE ON NEWER AGENTS

Earl Quijada MD and J Andrew Billings MD

Background Delirium is common in those with serious medical illness (See *Fast Fact* #1). Delirium is an acute change in mental status that fluctuates and has underlying physiologic causes and can be categorized as hyperactive, hypoactive, or mixed. Common reversible etiologies include constipation, urinary retention, medications (benzodiazepines, opioids, steroids, and anticholinergic drugs), electrolyte abnormalities, and sleep deprivation. Initial management strategies include identifying and treating the underlying cause, as well as non-pharmacological treatment. However, when these strategies are not effective pharmacological interventions may be necessary. The below pharmacological interventions are for potentially reversible, hyperactive delirium.

1st Generation Antipsychotics

Haloperidol Although no medication has been approved by the FDA for the treatment of delirium, the best studied antipsychotic, and the agent of choice for most patients, is haloperidol (Haldol), which can be administered safely through oral and parenteral routes. Starting doses are 0.5 – 1 mg PO or IV. Titration can occur by 2 – 5 mg every 1 hour until a total daily requirement is established, which is then administered in daily or twice daily doses. Recommended maximum dose is 100 mg/day. Intravenous haloperidol may cause less extrapyramidal symptoms than oral haloperidol.

Chlorpromazine Chlorpromazine (Thorazine) has more sedative effects than haloperidol for patients in whom sedation is desired. The starting dose is 25 - 50 mg PO. Titration can occur by 25 - 50 mg every 1 hour until a total daily requirement is established, which is then administered in daily or twice daily doses. Recommended maximum dose is 2000 mg/day.

2nd Generation Antipsychotics Also known as atypical antipsychotics, no evidence currently exists for improved efficacy with 2nd generation antipsychotics, so they are not considered to be first-line treatment. These agents are associated with fewer extrapyramidal side effects than 1st generation antipsychotics, hence, in Parkinson's disease and related neuromuscular disorders and in patients with a history of extrapyramidal reactions from 1st generation antipsychotics this class of agents may be preferred. For acutely agitated patients requiring onset of action within minutes, providers should know that these agents do not work as fast as conventional antipsychotics.

Olanzapine The starting dose for olanazapine (Zyprexa) is 5 mg PO every day; after one week, the dose can be raised to 10 mg a day; then to 20 mg a day. It is available as an orally disintegrating tablet.

Quetiapine Quetiapine (Seroquel) is initially given 25 mg PO twice a day which can be raised by 25 – 50 mg per dose every 2 – 3 days up to a target of 300 – 400 mg a day, divided into 2 – 3 doses. Compared to the atypical neuroleptics, it is the most sedating and causes the least extrapyramidal side effects. It has more orthostasis than olanzapine and risperidone.

Risperidone Resperidone (Resperidal) is given 1 – 2 mg PO at night and is gradually raised 1 mg every 2 – 3 days until an effective dose (usually 4 – 6 mg PO hs) is reached. It has minimal anticholinergic effects and does not cause orthostasis. It is the least sedating of this class of antipsychotics

Newer antipsychotics include ziprasidone (Geodon) and aripiprazole (Abilify); their role in the management of delirium is not firmly established.

Risks The FDA has issued a black-box warning about the increased risk of death when first- or

second-generation antipsychotics are used to treat dementia-related psychosis in elderly patients. This warning is based on a number of limited studies which have not been replicated and do not address the short-term use of antipsychotics to manage delirium. Delirium is a poor prognostic marker. Goals of care and values must be discussed in the management of delirium.

Benzodiazepines With the exception of treating delirium due to drug withdrawal or anticholinergic excess, benzodiazepines should be avoided for potentially reversible, hyperactive delirium unless the agitation is severe and uncontrolled by the neuroleptic. Benzodiazepines can make delirium worse and precipitate withdrawal syndromes.

Melatonin This hormone is produced naturally in the pineal gland and can help regulate the sleep-wake rhythm cycle. Randomized placebo-controlled trials have validated the use of both melatonin and a melatonin analog (ramelteon) in the prevention of delirium in at-risk, hospitalized patients.

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FAST FACTS AND CONCEPTS #81
MANAGEMENT OF HICCUPS

Chad Farmer MD

Background Hiccups (singultus) are distressing to patients and families; when chronic, they diminish quality of life. A hiccup is an involuntary reflex involving the respiratory muscles of the chest and diaphragm, mediated by the phrenic and vagus nerves and a central (brainstem) reflex center. A single episode can last for a few seconds to as long as several days. If they last longer than 48 hours hiccups are termed *persistent*; longer than one month, *intractable*. Etiologies range from stress/excitement to cancer, myocardial infarction, esophageal or gastric distension, liver disease, uremia, IV steroids, CNS lesions, chemotherapy, and idiopathic. Irritation of the vagus nerve or diaphragm is a common pathophysiologic mechanism.

Management Once hiccups have lasted beyond a time-limited annoyance, deciding on therapeutic intervention should be based on a thorough clinical assessment and, if possible, treatment directed at the underlying cause. A thorough history, review of medications, focused review of systems, and physical exam may help guide initial choice of treatment. Many drug and non-drug treatments have been used, but there is little evidence of any one superior approach to management; virtually all current data are anecdotal. The patient's prognosis, current level of function, and potential adverse effects from any proposed treatment should be considered.

Pharmacologic Therapy

- **Anti-Psychotics:** Chlorpromazine – the only FDA approved drug for hiccups. Dose: 25-50 mg PO TID or QID. Can also be given by slow IV infusion (25-50 mg in 500-1000 ml of NS over several hours). Haloperidol – a useful alternative to chlorpromazine; give a 2-5 mg (SubQ/PO) loading dose followed by 1-4 mg PO TID.
- **Anti-Convulsants:** Gabapentin – at doses of 300-400 TID has been described as effective in multiple case reports. Its dual role as an analgesic may make it an especially attractive therapeutic agent. Phenytoin – reportedly effective in patients with a CNS etiology of their hiccups. Dose: 200 mg slow IV push followed by 300 mg PO daily. Others: Valproic Acid and Carbamazepine have been reported to work for selected patients.
- **Miscellaneous:** Baclofen – the only drug studied in a double blind randomized controlled study for treatment of hiccups. 5 mg PO q8 hours did not eliminate hiccups but did provide symptomatic relief in some patients. Metoclopramide – 10 mg PO QID is an option, especially if stomach distension is the etiology. Nifedipine – 10 mg BID with gradual increase up to 20 mg TID has been suggested as a relatively safe alternative if other interventions have failed. Other drugs that have been tried with very limited success include: amitriptyline, sertraline, inhaled lidocaine, ketamine, edrophonium, methylphenidate, and amantidine.

Non-Pharmacologic Therapy There are many well known, time-honored home remedies: gargling with water, biting a lemon, swallowing sugar, or producing a fright response. Other approaches are directed at a) vagal stimulation such as carotid massage or valsalva maneuver; b) interruption of phrenic nerve transmission via rubbing over the 5th cervical vertebrae; or c) interrupting the respiratory cycle through sneezing, coughing, breath holding, hyperventilation, or breathing into a paper bag. Other interventions such as acupuncture, diaphragmatic pacing electrodes, or surgical ablation of the reflex arc can be considered when other treatments fail.

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PALLIATIVE CARE NETWORK OF WISCONSIN

FAST FACTS AND CONCEPTS #96
DIARRHEA IN PALLIATIVE CARE

Jeffrey Alderman MD

Diarrhea is a debilitating and embarrassing problem, defined as an abnormal looseness of the stools (increased liquidity or decreased consistency). Patients with uncontrolled diarrhea are at increased risk for dehydration, electrolyte imbalance, skin breakdown, and fatigue.

Common Causes Diarrhea can usually be divided into different types and treatment will vary depending on cause: secretory, osmotic, mechanical, or disordered motility. In palliative care, the overuse of laxatives, typically seen when the management of constipation is suddenly 'stepped-up,' is a common cause. Other causes include partial intestinal obstruction, pancreatic insufficiency, *Clostridium difficile* infection, and radiation enteritis. Chemotherapeutics are another common cause, especially in advanced cancer where the incidence can be up to 60% (diarrhea may be even more common with chemotherapy regimens with 5 flourouracil boluses or combination of irinotecan and fluoropyrimidines). Infectious diarrhea is especially common in HIV infection (*Cryptosporidia*, *Giardia lambila*, *E. histolytica*, and Cytomegalovirus). Severe constipation and fecal impaction can also cause diarrhea as backed-up, liquefied stool may be all that the patient can pass ('overflow diarrhea').

Evaluation Review diet, medications, laxatives, procedures, timing of movements in relation to ingestion of food or liquids, and a description of quantity and quality of stool. When performing a physical exam, make sure to palpate the abdomen and do a rectal exam. Radiographs are often not necessary, but may help clarify a partial bowel obstruction or overflow diarrhea. Keep in mind that patients at the end-of-life are also at risk for developing the same diarrheal illnesses that occur in the general population (viral/bacterial gastroenteritis, adverse effects of medications).

Treatment

- **General** Ensure adequate hydration; encourage sips of clear liquids; parenteral hydration should be considered for severe dehydration. Simple carbohydrates, toast or crackers, will add back small amounts of electrolytes and glucose; milk and other lactose-containing products should be avoided.
- **Medications** include bulk forming agents, antimicrobials, adsorbents, and opioids.
  - **Kaolin and Pectin** (Kaopectate®) is a suspension of adsorbent and bulk-forming agents, which can provide modest relief from diarrhea. However, kaolin-pectin may take up to 48 hours to produce an effect and can interfere with the absorption of certain medications.
  - **Antibiotics:** infectious diarrhea should be identified and treated with appropriate antibiotics, particularly *C. difficile* enteritis.
  - **Bismuth** has an additional antimicrobial effect, and can be added for increased symptomatic control against organisms such as enterotoxigenic *E. Coli.*
  - **Loperamide** (Imodium®), an opioid, reduces peristalsis in the gut, increases water reabsorption, and promotes fecal continence, making it a potent anti-diarrheal agent. Because it only weakly crosses the blood-brain barrier, loperamide's side effect profile is more favorable than other opioids (e.g. codeine or diphenoxylate [Lomotil®]). The initial dose of loperamide is 4 mg, with titration to 2 mg after each loose stool, with the typical dose being 4 – 8 mg per day. Although the package insert recommends a maximum of 16 mg in a 24-hour period, up to 54 mg per day of loperamide has been used in palliative care settings with few adverse effects. Note: loperamide should be used with caution if an infectious diarrhea is suspected.
  - **Aspirin** and **Cholestyramine** can reduce the diarrhea in radiation-induced enteritis, as can addition of a stool bulking agent such as psyllium (Metamucil™).
  - **Mesalamine** and other antiinflammatories are used for inflammatory bowel disease.
  - **Pancreatic Enzymes** such as pancrelipase are used for pancreatic insufficiency.
  - **Octreotide**, although costly, is effective with profuse secretory diarrhea seen in HIV disease, chemotherapy induced diarrhea, and those with high effluent volume from a

stoma. It may be given via continuous subcutaneous infusion at a rate of 10 – 80 mcg every hour until symptoms improve.
- **Budesonide, probiotics** and **activated charcoal** have been described in the literature for use in chemotherapy induced diarrhea, but there role in the clinical setting is not yet established.

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PCNOW PALLIATIVE CARE NETWORK OF WISCONSIN

FAST FACTS AND CONCEPTS #109
DEATH RATTLE AND ORAL SECRETIONS

Katherine Bickel and Robert Arnold MD

Background As the level of consciousness decreases in the dying process, patients lose their ability to swallow and clear oral secretions. As air moves over the secretions, which have pooled

in the oropharynx and bronchi, the resulting turbulence produces noisy ventilation with each breath, described as ‘gurgling ‘or ‘rattling noises.’ While there is no evidence that patients find this ‘death rattle’ disturbing, evidence from bereaved surveys suggests the noises can be disturbing to the patient’s visitors and caregivers who may fear that the patient is choking to death. However, similar sounds may occur in patients who are not imminently dying, such as in those with brain injuries or in patients with various disorders leading to increased production or decreased clearance of secretions. Two sub-types of the death rattle have been proposed, although the significance regarding treatment has not been established: Type 1 = predominantly salivary secretions and Type 2 = predominantly bronchial secretions. Death rattle is a good predictor of near death; one study indicated the median time from onset of death rattle to death was 16 hours.

Non-Pharmacological Treatments

- Position the patient on their side or in a semi-prone position to facilitate postural drainage
- A minute or two of Trendelenburg positioning can be used to move fluids up into the oropharynx for easier removal; aspiration risk is increased, however.
- Gentle oropharyngeal suctioning is used although this can be ineffective when fluids are beyond the reach of the catheter. Frequent suctioning is disturbing to both the patient and the visitors.
- Reduction of fluid intake.
- Communication with family and caregivers aimed to address associated fears and interpretations.

Pharmacological Treatments While multiple studies have questioned the utility of pharmacologic treatments for death rattle, muscarinic receptor blockers (anti-cholinergic drugs) are the most commonly used class of medication for this symptom. Such agents include scopolamine, hyoscyamine, glycopyrrolate, and atropine. All of these agents can cause varying degrees of blurred vision, sedation, confusion, delirium, restlessness, hallucinations, palpitations, constipation, and urinary retention. The primary difference in these drugs is whether they are tertiary amines which cross the blood-brain barrier (scopolamine, atropine, hyoscyamine) or quaternary amines, which do not (glycopyrrolate). Drugs which cross the blood-brain barrier are apt to cause CNS toxicity (sedation, delirium).

Drug	Trade Name	Route	Starting Dose	Onset
scopolamine (hyoscine) hydrobromide	Transderm Scop	Patch	One 1.5 mg patch	~12 h (24 h to steady state)
hyoscyamine	Levsin	PO, SL	0.125 mg	30 min
glycopyrrolate	Robinul	PO	1 mg	30 min
glycopyrrolate	Robinul	SubQ, IV	0.2 mg	1 min
atropine sulfate	Atropine	SubQ, IV	0.1 mg	1 min
atropine sulfate	multiple	Sublingual	1gtt (1% ophth. soln)	30 min

Pharmacological pearls

- Glycopyrrolate has five times the anti-secretory potency compared to atropine but is poorly and erratically absorbed orally. The clinical significance of this is unclear.
- The scopolamine patch releases ~1 mg over 72 hours. It takes 24 hours to reach steady state and for acute symptoms other drugs should be used. The patch should be placed on hairless skin just behind the ear, is changed every 72 hours, and more than one patch can be used at a time.
- Hyoscyamine is available in short-acting, sustained-released, orally dispersible tablet, and oral solution formulations.

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PALLIATIVE CARE NETWORK OF WISCONSIN

FAST FACTS AND CONCEPTS #114

MYOCLONUS

Nicholas DeMonaco and Robert Arnold MD

Background Myoclonus is an abnormal movement described as a sudden, brief, shock-like, involuntary movement caused by active muscle contraction (positive myoclonus) or inhibition of ongoing muscle contraction (negative myoclonus). Myoclonus can have a distribution that is focal, multifocal, or generalized. This *Fast Fact* discusses its causes, evaluation, and therapy.

Characteristics and Differential Diagnosis Hiccups are an example of normal, physiological positive myoclonus, while asterixis is an example of negative myoclonus seen with metabolic encephalopathy. In nocturnal myoclonus or periodic leg movement disorder, there is activity in the flexor muscles of the legs and feet during light sleep. It can be seen in the setting of chronic nervous system diseases or in elderly patients with no other abnormalities. The brief, shock-like movements of myoclonus may be difficult to distinguish from other involuntary movements such as cramps, spasms, fasciculations, and dystonia. Fasciculations are brief involuntary muscle twitches that, unlike myoclonus, often do not result in movement across a joint. Dystonia is characterized as slow, repetitive, patterned, sustained movements (an example is writers cramp). An acute dystonic reaction is often caused by dopamine blocking medications including certain antipsychotics (haloperidol), antiemetics (metoclopramide), and calcium-channel blockers.

Causes The etiologies of myoclonus are numerous. Near the end of life, metabolic abnormalities and medication-induced myoclonus predominate. Metabolic causes include liver failure, renal failure, hyponatremia, and hypoglycemia. The medications and toxins associated with myoclonus include opioids, anticonvulsants (gabapentin, phenytoin, valproate, lamotrigine, and phenobarbitol), tricyclic antidepressants and selective serotonin reuptake inhibitors, contrast dye, anesthetics, antibiotics (penicillins, cephalosporins, imipenem, and quinolones), cannabinoids and the chemotherapeutic agent ifosfamide. Opioid-induced myoclonus occurs commonly and is often misdiagnosed (See *Fast Facts* #57, 58). When myoclonus occurs due to toxins or medications, the jerks are usually multifocal or generalized, may be provoked by a stimulus or voluntary movement, and are often accompanied by encephalopathy. Other causes of myoclonus include focal CNS damage from tumors, stroke, and encephalitis, generalized CNS dysfunction such as encephalopathies (viral, metabolic, genetic, or neurodegenerative), seizure disorders, anoxic injury, and disorders affecting the spinal cord and peripheral nerves.

Treatment Myoclonus can disrupt sleep, make coordinated movements difficult, and be bothersome to patients or families. Treatment consists of correction of the underlying cause and symptomatic treatment of the myoclonus. If the offending agent is a non-essential medication, it should be discontinued. In the case of opioid-induced myoclonus, rotation to a different opioid may help. Benzodiazepines are the primary symptomatic treatment at end-of-life. While any benzodiazepine will work, clonazepam and lorazepam are commonly used. A continuous infusion of midazolam has also been suggested given the drug's compatibility with morphine and short half-life, allowing rapid dose titration. Sedation is likely when using benzodiazepines. If sedation is to be avoided, anticonvulsants such as levetiracetam (1,000-3,000 mg/day) and valproic acid (1200-2000 mg/day) may be helpful. The muscle relaxant dantrolene in doses of 50-100 mg/day has been reported as effective.

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PALLIATIVE CARE NETWORK OF WISCONSIN

FAST FACTS AND CONCEPTS #146
SCREENING FOR DEPRESSION IN PALLIATIVE CARE
Robert Arnold MD

Background Depression is a significant symptom for approximately 1 in 4 palliative care patients and is especially common in patients with metastatic cancer (see *Fast Fact* #21). Up to 80% of the psychological symptoms that occur in cancer patients go unrecognized and untreated. One reason for this is the difficulty in diagnosing depression in palliative care patients (see *Fast Fact* #7). In the primary care literature a number of brief screening instruments such as PRIME-MD are used to identify depression. However, the symptoms associated with depression in primary care (weight loss, loss of energy, fatigue, insomnia) also occur in patients without depression who have a life-threatening disease. Thus, there has been interest in developing a brief scale that can accurately identify depression in the palliative care population. This *Fast Fact* reviews that literature on depression screening tools.

Single question screening: A study of palliative care inpatients found that a single question, *"Are you feeling down, depressed or hopeless most of the time over the last 2 weeks?"* correctly identified patients with 100 percent sensitivity and specificity and a positive predictive value of 1 (Chochinov 1997). Adding a second question about anhedonia (the absence of pleasure from the performance of acts that would normally be pleasurable), *"Have you found that little brings you pleasure or joy over the last two weeks?",* reduced the specificity and positive predictive value. Unfortunately, follow-up studies using a single question regarding mood in other palliative care populations have shown a sensitivity of roughly 55 percent and a specificity of 75 percent.

A four-item algorithm asks questions about energy level, anhedonism, depressed mood, and psychomotor retardation/agitation. In a study of hospice patients in Australia this tool had a sensitivity between 62 and 72%, specificity of 75 to 89% and positive predictive value of between 68 and 89% (Robinson 2005).

The four question *Brief Case Find for Depression* asks questions about sleep, depressed mood, life satisfaction, and ability to overcome difficulties. In a study of oncology and palliative care patients this tool had fair agreement with longer depression screening instruments (Jefford 2004).

Other studies have examined 10-20 question depression instruments that have been validated in other patient populations. The ***Edinburgh Postnatal Depression Scale*** (Lloyd-Williams 2000), a self-assessment scale consisting of ten items each rated on a 4 point scale, had a sensitivity of 70% and specificity of 80% in patients with metastatic cancer receiving palliative care. The ***Hospital Anxiety and Depression Scale*** (Lloyd-Williams 2003) is a 14 item scale with separate sub-scales for anxiety and depression. In a group of patients with metastatic cancer, summing the two subscales gave a sensitivity of 77%, specificity was 89% and a positive predicted value of 0.48. Two more recent articles reported lower sensitivity and specificity in patients with advanced metastatic disease.

Summary and Recommendations

- Clinicians should have a high clinical suspicion for depression—especially in patients who exhibit feelings of hopelessness, worthlessness, guilt, anhedonia, sustained periods of feeling sad, and/or those with suicidal ideation and/or suicidal plans.
- The literature does not suggest that any of the above scales are clearly superior for helping to diagnose depression in a population of palliative care patients.
- Depression screening scales may be helpful in individual cases to provide the clinician with additional data in formulating a diagnosis; if used, it is suggested that clinicians be familiar with the sensitivity/specificity data for one scale and consistently use that scale so as to gain clinical familiarity.

- Psychiatric consultation is indicated in cases of diagnostic uncertainty and/or when patients present with profound depression and/or are overtly suicidal.

Definitions (Further resources available at: http://www.musc.edu/dc/icrebm/diagnostictests.html.)

- **Sensitivity:** The fraction of those with the disease correctly identified as positive by the test.
- **Specificity:** The fraction of those without the disease correctly identified as negative by the test.
- **Positive predictive value:** The fraction of people with positive tests who actually have the condition.

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PALLIATIVE CARE NETWORK OF WISCONSIN

FAST FACTS AND CONCEPTS #149
TEACHING THE FAMILY WHAT TO EXPECT WHEN THE PATIENT IS DYING

Charles F von Gunten MD, PhD

Introduction Family members look to the physician and nurse to help them know what to expect when a loved one is dying. No matter the underlying causes, there is a common final pathway that most patients travel. Indicate your desire to be helpful. Say, *Many families like to know what may happen so they will be prepared, is that true for you?* If they say yes, describe the features on this list and answer their questions.

1. **Social Withdrawal** is normal for the dying patient as the person becomes less concerned about his or her surroundings. Separation begins first from the world – no more interest in newspaper or television, then from people – no more neighbors visiting, and finally from the children, grandchildren and perhaps even those persons most loved. With this withdrawal comes less of a need to communicate with others, even with close family.

2. **Food:** The patient will have a decreased need for food and drink as the body is preparing to die. This is one of the hardest things for some family to accept. There is a gradual decrease in interest in eating and appetite—even for their favorite foods. Interest may come and go. The patient is not starving to death—this reflects the underlying disease. Liquids are preferred to solids—follow the patient's lead and do not force feed.

3. **Sleep:** The patient will spend more and more time sleeping; it may be difficult for them to keep their eyes open. This is a result of a change in the body's metabolism as a result of the disease. Tell family to spend more time with the patient during those times when he/she is most alert; this might be the middle of the night.

4. **Disorientation:** The patient may become confused about time, place and the identity of people around him/her. He/she may see people who are not there, such as family members who have already died. Sometimes patients describe welcoming or beckoning. While the patient may not be distressed, it is frequently distressing to family or health care professionals. Gently orient the patient if he or she asks. There is no need to 'correct' the patient if he or she is not distressed.

5. **Restlessness:** The patient may become restless and pull at the bed linens. These symptoms are also a change in the body's metabolism. Talk calmly and assuredly with the patient so as not to startle or frighten them. If the patient is a danger to himself or others, you may prescribe sedating neuroleptics (e.g.chlorpromazine), or neuroleptics (e.g. haloperidol) in combination with benzodiazepines (e.g. lorazepam), to help the patient rest (see *Fast Fact* #1).

6. **Decreased Senses:** Clarity of hearing and vision may decrease. Soft lights in the room may prevent visual misinterpretations. Never assume that the patient cannot hear you, as hearing is the last of the five senses to be lost.

7. **Incontinence** of urine and bowel movements is often not a problem until death is very near. Invite family to participate in direct care; the nurse can help place absorbent pads under the patient for more comfort and cleanliness, or a urinary catheter may be used. The amount of urine will decrease and the urine become darker as death becomes near.

8. **Physical Changes** as death approaches:

    a. The *blood pressure* decreases; the *pulse* may increase or decrease.
    c. The *body temperature* can fluctuate; fever is common.
    d. There is increased *perspiration* often with clamminess.
    e. The *skin color* changes: flushed with fever, bluish with cold. A pale yellowish pallor (not to be confused with jaundice) often accompanies approaching death.

f. *Breathing changes* also occur. Respirations may increase, decrease or become irregular; periods of no breathing (apnea) are common.
g. *Congestion* will present as a rattling sound in the lungs and/or upper throat. This occurs because the patient is too weak to clear the throat or cough. The congestion can be affected by positioning, may be very loud, and sometimes just comes and goes. Anticholinergic medications (like scopolamine or glycopyrrolate) can help (see *Fast Fact* #109). Elevating the head of bed and swabbing the mouth with oral swabs give comfort and give the family something to do.
h. The *arms and legs* may become cool to the touch. The hands and feet become purplish. The knees, ankles and elbows are blotchy. These symptoms are a result of decreased circulation.
i. The patient will enter a *coma* before death and not respond to verbal or tactile stimuli.

HOW TO KNOW THAT DEATH HAS OCCURRED

- No breathing and heartbeat.
- Loss of control of bowel or bladder.
- No response to verbal commands or gentle shaking.
- Eyelids slightly open; eyes fixed on a certain spot.
- Jaw relaxed and mouth slightly open.

Acknowledgement: This *Fact Fact* was adapted with permission from a family information handout (The 'Blue Sheet') given to families of San Diego Hospice & Palliative Care Program.

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XEROSTOMIA

Gary M Reisfield MD, Drew A Rosielle MD, and George R Wilson MD

Background Xerostomia (dry mouth) is a common symptom at the end of life – affecting more than 75% of hospice patients – and is a cause of significant morbidity and diminished quality of life. This *Fast Fact* will review the causes and treatments of xerostomia.

Salivary Functions include hydration, lubrication, and antimicrobial defense of the oral mucosa. Decreased salivation can lead to oral pain; accelerated dental morbidity; oral infections, fissures, and ulcerations; halitosis; alteration in taste and enjoyment of food; chewing and swallowing difficulties; nutritional impairment; trouble producing intelligible speech; and denture-related problems. Xerostomia is usually—although not always—associated with diminished salivary secretion (hyposialia).

Etiologies

- *Medications* with anticholinergic activity are the most common pharmacologic causes of xerostomia; these include many antiemetics, antihistamines, antipsychotics, antispasmodics, antidepressants (especially the tricyclics), and bronchodilators. Sympatholytics are also common culprits, including alpha-blockers (e.g. terazosin), alpha-2 agonists (e.g. clonidine), and beta-blockers (e.g. metoprolol). Medication-induced xerostomia may also result from direct interference with or damage to salivary tissue (as with some cancer chemotherapies). Opioids and benzodiazepines cause dry mouth, although the mechanisms are not known.
- *Radiation* for head and neck malignancies.
- *Medical comorbidities* such as HIV/AIDS, diabetes, renal failure, and Sjögren's syndrome.
- *Psychiatric comorbidities* such as mood and anxiety disorders.
- *Dehydration* from any cause including drug-induced.

Treatment

- **Address underlying causes.** Eliminate unnecessary drugs or substitute less drying ones. If this is not feasible, titrate to lowest effective dose or modify dosing schedule. Replacing immediate-release with controlled-release formulations of some drugs may help (e.g. with oxybutynin and tolterodine for overactive bladder).
- **Stimulate residual gland function.**
    - *Sugarless gums and candies* can stimulate salivary reflexes. Products sweetened with xylitol are anticariogenic; those containing vitamin C may reduce salivary viscosity.
    - *Cholinergic agonists* such as pilocarpine and cevimeline. Therapeutic effect is rapid for drug-related xerostomia; latency is greater (often 8-12 weeks) for xerostomia related to radiotherapy. Pilocarpine is started at 5 mg po tid and can be titrated to 10 mg po tid. Cevimeline is dosed at 30 mg po tid. Urinary frequency, dizziness, and sweating are common side effects and may be attenuated with intake of dairy products. These agents are contraindicated in asthma, acute iritis, and narrow-angle glaucoma, and should be used with caution in COPD and cardiac disease.
- **Saliva substitutes.** Most have limited efficacy; many patients find frequent sips of water more useful and convenient. Topical products containing olive oil, betaine, and xylitol have been found effective for medication-induced xerostomia (e.g. Xerostom® products). Newer products with enzyme systems such as lactoperoxidase, lysozyme, and glucose oxidase (e.g. Biotène® Oralbalance Dry Mouth Gel)—offer potential antimicrobial and moisturizing benefits. Due to limited duration of action, they may be particularly useful before eating, speaking, and sleeping. Recently, custom oral appliances with artificial saliva reservoirs have become available and may be particularly useful at night.
- **Encourage oral hydration**. Humidifiers, especially during sleep, may also be helpful.
- **Optimize oral hygiene.**
    - Antimicrobial mouthwashes (alcohol-free). Chlorhexidine gluconate oral rinse, USP 0.12%, twice daily, may be effective in preventing dental caries and oral infections**.**
    - Most toothpaste products contain the surfactant sodium lauryl sulfate (SLS), which can irritate dry mucosa and inactivate the enzyme systems of the newer artificial salivas. Biotène® Dry Mouth Toothpaste contains salivary enzymes and is SLS-free.

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PALLIATIVE CARE NETWORK OF WISCONSIN

FAST FACTS AND CONCEPTS #186
ANXIETY IN PALLIATIVE CARE – CAUSES AND DIAGNOSIS

Joseph Stoklosa, Kevin Patterson MD, Drew Rosielle MD, and Robert Arnold MD

Background *Anxiety* is a state of apprehension and fear resulting from the perception of a current or future threat to oneself. The term is used to describe a *symptom* and a variety of *psychiatric disorders* in which anxiety is a salient symptom. This *Fast Fact* will discuss the causes and evaluation of anxiety.

Prevalence Anxiety is commonly reported in those facing life-threatening illnesses. At least 25% and cancer patients and 50% of CHF and COPD patients experience significant anxiety. At least 3% of patients with advanced cancer and 10% of COPD inpatients meet DSM criteria for Generalized Anxiety Disorder (see below).

Etiologies
- Anxiety may be present as part of one of several psychiatric disorders (see below).
- Anxiety is often a prominent component of acute or chronic pain, dyspnea, nausea, or cardiac arrhythmias.
- Adverse drug effects: corticosteroids, psychostimulants, and some antidepressants.
- Drug withdrawal: alcohol, opioids, benzodiazepines, nicotine, clonidine, antidepressants, and corticosteroids.
- Metabolic causes: hyperthyroidism and syndromes of adrenergic or serotonergic excess.
- Existential and psychosocial concerns about dying, disability, loss, legacy, family, finances, and religion/spirituality.

Psychiatric Disorders with anxiety as a prominent symptom
- **Generalized anxiety disorder** is a psychiatric disorder characterized by pervasive and excessive anxiety and worry about a number of events or activities (such as work or school performance), occurring more days than not for at least 6 months. The anxiety and worry are associated with at least 3 of the following 6 symptoms: restlessness, easy fatigue, difficulty concentrating, irritability, muscle tension, and sleep disturbance.
- **Panic disorder** is characterized by recurrent panic attacks. See *Fast Fact* #145 for its evaluation and management.
- **Adjustment disorder** occurs within 3 months of a major stressor, and causes marked distress and functional impairment. Usually it is characterized by a depressed mood but anxiety can also be its most prominent affective component.
- **Acute- or post-traumatic stress disorders** occur after an emotionally traumatic life-event and are characterized by anxiousness and arousal, as well as by numbness, flashbacks, intrusive thoughts, and avoidance of stimuli which remind the patient of the trauma.
- **Phobias** are marked, persistent fears brought about by specific situations or objects.

Evaluation
- Complete a thorough history and physical exam, in particular ask about:
  - Prior episodes or anxiety, depression, PTSD, alcohol, and drug use.
  - Prior and current treatment by a mental health professional.
  - Presence of specific trigger situations or thoughts leading to anxiety.
  - Presence of apprehension, dread, insomnia, and hypervigilance; as well as physical symptoms such as diaphoresis, dyspnea, muscle tension, and tremulousness.
- Seek help from a professional familiar with the psychiatric disorders when anxiety is a prominent and functionally impairing part of a patient's symptoms.
- Symptoms that can be confused with anxiety are agitated delirium (see *Fast Facts* #1,60) and akathisia, an unpleasant sense of motor restlessness from dopamine-blocking medications such as antipsychotics and some antiemetics.
- Formal screening tools exist, but there is no consensus on the benefit of their routine use. Commonly used tools which evaluate for anxiety as a symptom include the Edmonton

Symptom Assessment Scale, the Memorial Symptom Assessment Scale, and the Hospital Anxiety and Depression Scale.

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PALLIATIVE CARE NETWORK OF WISCONSIN

FAST FACTS AND CONCEPTS #199
OPIOIDS FOR COUGH

Sean Marks MD and Drew A Rosielle MD

Background Cough is a common, and at times distressing, symptom. Up to 40% of advanced cancer patients report cough, and while a smaller percentage find their cough distressing, severe cough can lead to dyspnea, nausea/vomiting, sleep impairment, chest and throat pain, and impaired communication. This *Fast Fact* will focus on the use of opioids for the symptomatic treatment of cough. *Fast Fact* #200 will address other agents for cough.

Etiologies & Evaluation Common etiologies of cough include infections of the upper and lower airway, asthma and COPD, lung cancer or lung metastases, interstitial pulmonary processes (such as lymphangitic tumor spread or pulmonary edema), gastroesophageal reflux, aspiration, and drugs. Common drug causes include ACE inhibitors, NSAIDs, and inhalant medications. Evaluating for reversible causes is appropriate if consistent with the goals of care and prognosis. If feasible, treatment should be directed at the underlying cause. Many patients however will benefit from symptomatic therapy for a distressing cough while waiting for acute therapy to work or have a chronic cough not amenable to treatment (e.g. cough due to advanced lung cancer).

Opioids are the only clearly effective centrally-acting anti-tussive drugs and are thought to work by suppressing the brainstem cough center through mu and kappa opioid receptor agonism. They are the first-line symptomatic treatment for severe, distressing cough. All opioids used to treat cough have typical opioid side effects such as sedation, constipation, and nausea.

- *Codeine:* Duration of action is 4 hours; usual adult dose is 10-20 mg every 4-6 hours. It has shown to be effective for acute and chronic cough in several placebo-controlled trials. It is available alone or as an elixir with guaifenesin.

- *Dextromethorphan:* Duration of action 3-6 hours; usual adult dose is 10-20 mg every 4-6 hours. It is the most commonly used anti-tussive. Confirmed to be as effective as codeine for cough in multiple studies. It is available alone or as an elixir with guaifenesin. Note: dextromethorphan inhibits the cytochrome P450 system and thereby affects the metabolism of many drugs. Dextromethorphan can also cause a serotonin syndrome if used with serotonergic drugs such as antidepressants.

- *Hydrocodone:* Duration of action 4-6 hours; usual dose 5-10 mg every 4 hours. Hydrocodone is only available as a combination product in the US: as a short-acting elixir with the anticholinergic drug homatropine or as an extended release elixir with the antihistamine chlorpheniramine (dosed at 10 mg every 12 hours). These other agents magnify hydrocodone's sedative effects, and limit the maximum dose a patient can take. Hydrocodone has been shown to be as effective as codeine in head to head studies but with fewer gastrointestinal side-effects. For this reason it is considered by many experts as the anti-tussive of choice (Homsi 2001).

- *All opioid* analgesics have anti-tussive activity and their use has been mostly based on convention; there is no strong evidence that any one opioid has superior efficacy for cough. For patients already taking opioids for pain, it is unclear whether adding a second opioid such as codeine for cough is effective. One uncontrolled, open-label study showed hydrocodone to be helpful in this setting; it has not been repeated (Homsi 2001).

Fast Fact #200 will discuss non-opioid agents for cough, as well as address some general treatment strategies.

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PALLIATIVE CARE NETWORK OF WISCONSIN

FAST FACTS AND CONCEPTS #200
NON-OPIOID ANTI-TUSSIVES

Sean Marks MD and Drew A Rosielle MD

Background Cough is a common and at times distressing symptom. *Fast Fact* #199 discussed opioids for the symptomatic treatment of cough. This *Fast Fact* will address non-opioid anti-tussives.

Controversies Commonly used prescription and over-the-counter anti-tussive formulations which contain some combination of antihistamines (e.g. diphenhydramine), a mucolytic (e.g. guaifenesin), and/or dextromethorphan are often used for acute cough due to upper respiratory infections and acute bronchitis. Evidence for these agents in the acute setting is poor (either no better than placebo or sweet syrup) and cannot be recommended. Due to concerns about inadvertent overdose and lack of efficacy, these products are now being *actively* discouraged for use in the pediatric setting.

Centrally-acting non-opioid anti-tussives

- *Gabapentin:* the pathophysiology of refractory chronic cough is thought to resemble central sensitization as seen in neuropathic pain. A randomized, double-blind placebo controlled trial demonstrated that gabapentin can meaningfully improve cough-specific quality of life and reduce cough frequency and severity compared with placebo. Doses up to 1800 mg a day were studied.
- *Other neuromodulating agents*: paroxetine, amitriptyline, and benzodiazepines have been anecdotally reported to have efficacy in chronic, refractory cough but lack published controlled evidence.

Peripherally-acting anti-tussives

- *Sweet syrups* are commonly used as cough suppressants, whether as bases for prescription elixirs (such as codeine with guaifenesin) or home remedies (honey, simple syrup). The mechanism of action is unknown; some authors hypothesize it acts as a protective barrier to sensory receptors in the throat that heighten the cough reflex. A few controlled trials have shown sweet syrups reduce coughing in upper respiratory infections.
- *Benzonatate* inhibits cough by anesthetizing stretch receptors in the respiratory tract. Its duration of action is 3-8 hours; dosed at 100-200 mg three times a day. No published controlled studies confirm its effectiveness but multiple uncontrolled studies support its use. Side effects are uncommon but include sedation, headache, bronchospasm, and nausea. Empirically many experts recommend adding it to an opioid.
- *Antihistamines and anticholinergics* are often part of combination anti-tussive elixirs with or without an opioid. Anticholinergics such as hyoscyamine and scopolamine are most helpful in the setting of copious upper respiratory secretions leading to cough. See *Fast Fact* #109 for dosing information.
- *Expectorants* thin bronchial secretions and ease expectoration. Examples include guaifenesin (200-400 mg every 4 hours) and nebulized acetylcysteine or hypertonic saline. Empirically they have been recommended for severe, chronic, wet coughs. Because they may increase fluid in the respiratory tract, they are not recommended if the cough reflex is diminished.
- *Nebulized local anesthetics* are thought to work by anesthetizing afferent receptors in the respiratory tract. There have been no trials evaluating their effectiveness; anecdotally they have been reported to be effective for refractory cough. Published regimens include lidocaine 2% solution, 5 mL nebulized every 6 hours; and bupivacaine 0.25%, 5 mL nebulized every 8 hours. Bronchospasm is a potential side effect.
- *Other agents* such as bronchodilators and corticosteroids have not been shown to be effective apart from specific indications (e.g. for COPD or asthma exacerbations).

Recommendations Treatment for cough should be directed at the underlying cause if feasible and consistent with a patient's prognosis and goals of care. When symptomatic treatment for a distressing cough is necessary, it is reasonable to start with an opioid product, adding benzonatate if needed. A trial of anticholinergics and expectorants for the indications described above is reasonable, but they should be stopped after a couple days if they have no effect. Sweet syrups appear to be helpful in upper respiratory infections; their role otherwise is uncertain. If these strategies fail to control distressing symptoms, gabapentin should be tried for chronic cough.

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PALLIATIVE CARE NETWORK OF WISCONSIN

FAST FACTS AND CONCEPTS #218
MANAGING WOUND ODOR

Bansari Patel APN and Deon Cox-Hayley DO

Background Foul-smelling non-healing wounds are common in patients nearing the end-of-life, whether from pressure ulcers, vascular disease, or tumors. Strong wound odors can lead to social and physical isolation, altered patient body image and self-worth, and can challenge caregivers. This Fast Fact will discuss a practical approach to ameliorating wound odors. See also *Fast Facts* #40 and #41 (pressure ulcers), #46 (malignant wounds), and #185 (topical opioids).

Pathophysiology Foul odors from wounds result from the metabolic by-products of anaerobic and certain gram negative organisms. Deeper infection (e.g. cellulitis, necrotizing infections) are not necessary for significant odor generation.

Management While it should be addressed, treatment of the underlying cause of the wound is often limited in patients with advanced illnesses. In all circumstances, attempts at ameliorating wound odor are important – whether by treating the cause of the odor or hiding the odor.

- Addressing the cause of the odor:
  - *Remove the wound bed contaminants* (e.g. debride the wound of necrotic tissue).
  - *Control infection*. There are several approaches, all aimed at controlling anaerobic growth.
    - Topical Metronidazole is available as a commercially produced gel. Metronidazole functions as an anti-inflammatory as well as anti-infective agent against anaerobes which reduces odors. Metronidazole gel is applied directly to the wound once or twice daily. Studies have shown decreases in wound odor in 2-3 days, and application is usually continued for up to 2 weeks. Courses can be repeated if needed. In one study, 63% of patients had complete eradication of odor after a course of metronidazole gel, with the remainder reporting improvements. Costs can range from a few dollars for compounded gels to ~$90-150 for 45 gm of commercial gel. Metronidazole tablets can also be broken and the powder contents sprinkled into the wound. Applying dressings soaked in a mixture of normal saline and intravenous metronidazole solution has also been reported as helpful for controlling odor.
    - Systemic Metronidazole can be used if there is evidence of deep tissue infection causing foul odor. 500 mg 3 or 4 times daily IV or orally is used, instead of or in addition to topical metronidazole. Systemic side effects such as nausea and diarrhea can occur.
    - Topical Silver Sulfadiazine ($4-$20) has been shown to be helpful in controlling odors of superficial wounds. In several studies, silver containing dressings were more effective than nonsilver dressings in reducing odors.
    - Cadexomer Iodine is an antimicrobial agent containing slow release iodine and has been shown to decrease bacterial counts and odor from venous ulcers. Ointment, powder and impregnated bandage forms are available. Cadexomer iodine has the added benefit of absorbing exudate and can be particularly helpful when exudate absorption and odor control are both needed. It can cause a burning sensation upon application.
    - Yogurt or buttermilk, applied for 15 minutes after a wound is cleaned, have been reported to control malignant wound odor, though studies are limited. They are thought to control bacterial proliferation by lowering a wound's pH.
    - Honey can be bacteriocidal, and has been increasingly studied for wound healing. There is some evidence that it may be effective in managing odor as well as wound pain.
- Hiding the odor:
  - Aromatics: Scented candles, air freshener sprays, peppermint and other essential oils, coffee beans or grounds, and cider vinegar in a pan are all used to hide odors.

- Adsorbents: Charcoal adsorbs aromatic molecules. A basket of charcoal (briquettes) can be placed discreetly in a patient's room. Various commercially available charcoal dressings are also available, although expensive. These dressings are applied over the primary dressing and may be re-used as long as they remain dry. Baking soda can be applied between dressing layers to help absorb odor. Cat litter can also be used similarly to charcoal briquettes.

Support and Education There can be great psychosocial distress associated with malodorous wounds: embarrassment, shame, and isolation. In addition to wound care specialists, psychological and spiritual support services can be important in helping patients and families cope with a chronic wound. Educate the patient and caregivers about the management of chronic wounds, and commit to controlling odor as much as possible. Health care providers should be trained to avoid demonstrating distress at odors in front of or in hearing distance of patients or families.

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Author Affiliations: University of Chicago, Chicago, Illinois.

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official prescribing information should be consulted before any such product is used.

PALLIATIVE CARE NETWORK OF WISCONSIN

FAST FACTS AND CONCEPTS #229
SEIZURE MANAGEMENT IN THE DYING PATIENT
Jennifer Connelly MD and David E Weissman MD

Background Seizure management in the dying patient without intravenous (IV) access, such as is in the home environment, is challenging. In this population they can be due to primary or metastatic brain cancers, strokes, toxic/metabolic causes like hypoglycemia, or pre-existing epilepsy. The incidence of seizures in dying patients is unknown, and while likely uncommon, they can cause tremendous distress to patients and families. This *Fast Fact* reviews management strategies for seizures near the end of life.

Seizure Prophylaxis Up to 40% of patients with brain tumors have a seizure at the time of diagnosis and another 20% eventually develop seizures. Although antiepileptic drugs (AEDs) are commonly started as prophylaxis at the time of brain tumor diagnosis, they have not been found to prevent seizures and the American Academy of Neurology Clinical Practice Guidelines do not support this practice (1). Thus, prophylactic AEDs can be safely discontinued in patients with brain tumors who have never had a seizure. For brain tumor patients with a seizure history (especially those with a history of status epilepticus), AEDs should be continued when possible. In one study, tapering AEDs in the last week of life was associated with seizures in 35% of patients with high-grade gliomas. For patients who lose an enteric route and have no intravenous access, rectal administration of prophylactic AEDs is possible. Clinical judgment should be used as to whether to continue AEDs in this setting as it can be appropriate to simply stop them, particularly if the patient's prognosis is very short. Phenobarbital, pentobarbital, carbamazepine, valproic acid, and lamotrigine can all be given rectally. Rectal absorption of other prophylactic AEDs is undefined and they should not be administered. No AEDs need dose adjustments for rectal administration. Carbamazepine should be divided into small doses administered 6-8 times a day. Lamotrigone is administered rectally by crushing and suspending the chewable tablets in 10 mL of water. When clinically indicated, drug levels of lamotrigine should be monitored as rectal absorption is erratic. There is no data for the use of rectal levetiracetam in humans.

Seizure Management

- Single self-limited seizure: Check for treatable causes such as hypoglycemia. If no reversible cause is identified, initiation of maintenance AED therapy should be considered, particularly if the patient is expected to survive more than a few weeks.
- Acute seizure or status epilepticus:
  - Non-IV routes: Studies, mainly in the pediatric population, have shown intranasal (IN) midazolam at a dose of 0.2 mg/kg to be an effective and convenient agent to abort an acute seizure. It has a quick onset of action of only 4-8 minutes and a time to maximal concentration of 15-30 minutes. Rectal diazepam (0.3 mg/kg) used to be the drug of choice for this indication and can be considered, but it has a longer onset of action, is more expensive, and appears to be less preferred by patients compared with IN midazolam. Once the initial seizure is controlled, diazepam 20 mg PR nightly should be considered to reduce the occurrence of further seizure events. Other rectal benzodiazepines are available (clonazepam, lorazepam, and midazolam), but take longer to reach peak serum levels. Sublingual lorazepam is also available, but is not well-studied.
  - IV routes: When available, IV or subcutaneous (SC) benzodiazepines should be used to stop a seizure in progress; IV lorazepam is preferred due to its onset of action and half-life. SC dosing is equivalent to IV for lorazepam, midazolam, and clonazepam. If seizure activity persists, additional anti-epileptic medication should be provided using a loading and then maintenance dose. Patients with refractory seizures who have short prognoses and comfort-oriented goals of care should be considered for an anti-epileptic sedative such as a continuous midazolam or barbiturate infusion with the goal of deep sedation (see *Fast Facts* #106,107).

Parenteral AED Dosing and Routes.

Drug	**Status loading dose**	**Maintenance dose**
Diazepam	0.2 mg/kg or 10-20 mg PR	20 mg PR nightly
Lorazepam	0.1 mg/kg IV, IM, or SC	
Midazolam	0.1-0.3 mg/kg IV or SC	Titrate to control refractory seizures if needed
Clonazepam	1 mg IV or SC	
Phenytoin	20 mg/kg IV	4-5 mg/kg/day IV divided TID
Fosphenytoin	20 mg/kg IV or IM	4-5 mg/kg/day IV or IM divided TID
Phenobarbital	10-15 mg/kg	1-3 mg/kg/day IV or IM 1200 mg/day SC (2)

*** Levetiracetam: Doses up to 2,500 mg IV have been used successfully and safely when added to standard status epilepticus regimens. A typical maintenance dose is 500-1500 mg PO or IV BID.**

Family Education Family members should be counseled that all medications used to manage seizures can cause sedation and cardiopulmonary depression. Family members who have witnessed prior seizures often have great fear about seizure recurrence. Many hospice agencies have established seizure protocols and medication kits which can be stored at home, and will collaborate with physicians and families on establishing a 'seizure plan' for acute seizures. Review seizure safety with families, including not putting anything in the patient's mouth and making sure the patient is in a safe environment.

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Author Affiliations: Medical College of Wisconsin, Milwaukee, WI.

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FAST FACTS AND CONCEPTS #256
FEVER NEAR THE END OF LIFE

Mallory Strickland BS and Erica Stovsky MD

Introduction Clinically significant fever is defined as an increase in body temperature (generally > 38.5°C) in conjunction with an elevation of the hypothalamic set point. Hyperthermia is an uncontrolled elevation in body temperature without a change in the thermoregulatory center. This *Fast Fact* reviews the key elements in assessment and treatment of fever in patients near the end-of-life.

Pathophysiology Fever is mediated by exogenous pyrogens (microbes or their products) and pyrogenic cytokines (i.e. IL-1,IL-6, IFN a, TNF) which induce the synthesis of prostaglandin E2 (PGE2). Centrally, PGE2 increases production of cAMP, which raises the hypothalamic set point to febrile levels. Peripherally, this induces myalgias and arthralgias. Pyrogens/pyrogenic cytokines are produced by infection, inflammation, trauma/tissue necrosis, and tumors. Drugs can induce fever through various metabolic and immune responses as well as by mimicking endogenous pyrogens, inflicting direct tissue damage and interfering with heat loss. Common drugs in palliative care settings which cause fever include antibiotics, anti-psychotics (neuroleptic malignant syndrome) and opioid withdrawal. Fever associated with brain injuries is common, perhaps due to direct hypothalamic injury.

Assessment The extent of evaluation will depend on the patient's condition and overall goals of care. When indicated, a thorough history and physical exam is needed, looking for a) signs of infection, b) in cancer patients, evidence of disease progression, and c) a medication review. A typical infection laboratory and radiographic workup can be pursued if it will affect management. Common etiologies and clinical findings are reviewed below.

- Infection: look for a history of exposure (e.g. influenza), normal barrier violation (e.g. aspiration, skin ulcer), and neutropenia (for instance, if receiving chemotherapy). Associated signs/symptoms include elevated WBC, chills, spiking temperatures, and if severe, hypotension, tachycardia, mental status changes and neutropenia. **Note:** Newborns, the elderly, patients with chronic hepatic or renal failure, the immunocompromised, and those taking glucocorticoids can have serious infections without a fever.
- Neoplastic Fever: a diagnosis of exclusion. It is uncommon in solid tumors, more common in lymphomas. It is less likely to manifest as chills, hypotension, tachycardia, and mental status changes; however elevated ESR and CRP are common. It tends to be responsive to NSAIDs.
- Medication-Induced: there is no predictable time of onset from medication initiation to fever presentation. It resolves when suspected drug is stopped.
- DVT/PE: thought to cause fever through inflammation. Fever is inconsistently associated with DVT/PE in the literature, however these are common events in the end-of-life population.

Treatment Benefits and burdens of all therapeutic options should be weighed in the context of the patient's overall clinical picture, including whether a fever is actually distressing to a dying patient. When deciding *if* to treat the fever, ask patients who can communicate if the fever is uncomfortable, and whether or not breaking the fever is more uncomfortable than the fever itself. Although empiric, there is no compelling reason to think that treatment of fever actually reduces suffering for dying, unresponsive patients. *Education* and *reassurance* for family and other caregivers is most important in those situations.

- **Non-pharmacological Interventions**
  - Cooling blankets, ice packs, sponging, and fans. While these can bring down body temperature, they are noisy, labor-intensive, and distract family and other caregivers from more meaningful interactions at the death-bed.
- **Pharmacologic Interventions**
  - Discontinue any non-essential drugs if drug-induced fever is suspected.
  - Antipyretics work by inhibiting production of PGE2. Acetaminophen 650-1000mg* PO/PR/IV q4-6 hours PRN (maximum dose 4 g/day*) is considered first line given its low side effect profile. NSAIDs (oral, IV, rectal, subcutaneous) are also effective. Naproxen 250mg* q12hrs is particularly effective in neoplastic fever, and possibly diagnostic when

infection is ruled out. The order can state “PRN for symptomatic fever” to discourage focus on the temperature measurement alone.
    - Antibiotic therapy has been shown to be inconsistently useful in alleviating fever symptoms in terminally ill patients. While evidence is unclear as to the utility of providing antibiotic therapy, discussions should address their use as a potential treatment that may or may not improve symptoms and prolong life/delay death; time-limited trials can be appropriate.
    - Glucocorticoids (oral, IM, IV) are also purported to be effective, however most of the data supporting their use exist in the neurological and head injury literature.

*****Discussed doses are for adults.

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Authors’ Affiliation Drexel University College of Medicine, Philadelphia, PA (SM); University of Pittsburgh Medical Center, Pittsburgh, PA (ES).

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PALLIATIVE CARE NETWORK OF WISCONSIN

FAST FACTS AND CONCEPTS #309
PHARMACOLOGIC MANAGEMENT OF DEPRESSION IN ADVANCED ILLNESS
Leah Rosenberg, MD; Jane deLima Thomas, MD

Adults with serious illness have a higher incidence of major depressive disorders than healthy adults, with an estimated incidence of 15% (1). In this *Fast Fact*, we will provide a clinical framework for selecting pharmacologic agents for seriously ill patients with depression. See *Fast Facts* # 7, 43 and 146 for assistance in diagnosing and screening for depression in palliative care patients.

Determine the patient's prognosis Because most traditional antidepressants take more than 4 weeks to become effective, they should only be considered in patients expected to live at least that long (2). Use is also limited to patients who are able to swallow oral medications or place them in a feeding tube. For patients with a prognosis < 4 weeks, a psychostimulant such as methylphenidate or dextroamphetamine may act within 1-2 days and be safe in patients without significant cardiovascular disease or delirium. Although the data on psychostimulants are somewhat mixed, controlled trials have shown benefit as both a monotherapy or to augment the effects of another anti-depressant (3-5). See *Fast Fact* #61.

Consider co-morbid symptoms When choosing an antidepressant, consider the patient's other co-morbid symptoms such as insomnia, neuropathic pain, or poor appetite (6). Other considerations include the patient's past responses to specific agents and possible drug interactions. Common classes of antidepressants include serotonin-selective reuptake inhibitors (SSRIs), serotonin-selective norepinephrine reuptake inhibitors (SNRIs), tricyclic antidepressants (TCAs), and others.

SSRIs Also called "second generation antidepressants", these are the most commonly prescribed antidepressants. SSRIs should be started at a low dose and then titrated to the minimum effective dose to minimize adverse effects such as QTc prolongation, sexual dysfunction, headaches, nausea and diarrhea. Fluoxetine is associated with emotional activation and may worsen anxiety. Paroxetine can be sedating and lead to withdrawal phenomena with missed doses. Because sertraline, citalopram, and escitalopram have lower side effect profiles and are neither activating nor sedating, they may be better choices for palliative care patients (7). The starting dose of sertraline is 25-50 mg/day with a usual effective dose of 50-200 mg/day; it is available in a concentrated liquid formulation for patients with dysphagia related issues. Both citalopram and escitalopram have been shown to have few drug interactions. The starting dose of citalopram is 20 mg/day with a maximum daily dose of 40 mg. The starting dose of escitalopram is 10 mg/day with a usual effective dose of 10-20 mg/day (8-10).

SNRIs inhibit serotonin and norepinephrine reuptake, two neurotransmitters important in endogenous pain pathways (11). This class may be helpful for neuropathic pain, vasomotor instability, and anxiety-predominant depression. In particular, venlafaxine has shown effectiveness for the amelioration of hot flushes and the prevention of chemotherapy-induced polyneuropathy (CIPN); duloxetine has shown efficacy for the treatment of CIPN (12). SNRIs may prolong bleeding times and therefore may not be safe in patients with active bleeding or intracranial metastases. The starting dose for venlafaxine is 37.5 mg with a usual effective dose of 75-225 mg/day. It requires close monitoring for missed-dose withdrawal and hypertension. The starting dose for duloxetine is 30 mg with a usual effective dose of 60-120 mg/day. It has been associated with hepatic insufficiency and a worsening of acute-angle glaucoma.

TCAs are an older class of anti-depressants that can be cost-effective when used at lower doses. They also are proven adjuvant analgesics for neuropathic and chronic low back pain. Unfortunately, their anticholinergic properties can induce delirium, prolong the QTc interval, and be dangerous in overdose. Therefore, their use is limited to heart-healthy patients under the age of 65 with comorbid neuropathic pain and insomnia. Although the preponderance of supporting data for the analgesic effects is for amitriptyline (usual starting dose 10-25 mg/day; usual effective dose is 150 mg/day), nortriptyline is felt to be less sedating (usual starting dose 25 mg/day; usual effective dose is 50-100 mg/day).

Other Medications **Mirtazapine** has histaminergic side effects that can be helpful especially for cancer patients who often experience insomnia, poor appetite, and nausea (13). It has few drug interactions but can be associated with orthostatic hypotension. Its usual starting dose is 7.5-15 mg/nightly; usual effective doses are 15-30 mg/day. **Buproprion** is thought to be less sedating and have a lower incidence of sexual side effects, but it may lower the seizure threshold. The usual starting dose for buproprion is 150 mg/day; the usual effective dose is 150-300 mg/day (14). **Single-dose treatment with NMDA antagonist ketamine** has shown promise in early investigational studies (15). **Aripiprazole** may augment the antidepressant effects of SSRIs and SNRIs as early as a week after initiation (16).

Summary Recommendations:

- For patients with prognoses of weeks, consider the use of a psychostimulant like methylphenidate.
- Consider duloxetine or venlafaxine when neuropathic pain is present.
- When polypharmacy is present, consider citalopram, escitalopram or mirtazapine.
- If the patient has insomnia, nausea, or anorexia, consider the use of mirtazapine.
- Closely monitor patients initiated on an antidepressant for adverse effects and dose titration.
- Refer to a mental health clinician for pre-existing major depression, the presence of comorbid psychiatric illness, suicidal ideation, refractory symptoms, or psychiatric polypharmacy.
- Refer to social work and/or spiritual support services if the depression appears to be escalating in relation to social or spiritual factors.

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Author Affiliations: Massachusetts General Hospital and Dana-Farber Cancer Institute, Boston, MA.
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