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Selected Topics: Oncological Emergencies

ONCOLOGIC EMERGENCIES: PALLIATIVE CARE IN THE EMERGENCY DEPARTMENT SETTING

Drew A. Long, MD,* Alex Koyfman, MD,† and Brit Long, MD*

*Department of Emergency Medicine, Brooke Army Medical Center, Fort Sam Houston, Texas and †Department of Emergency Medicine, The University of Texas Southwestern Medical Center, Dallas, Texas

Reprint Address: Brit Long, MD, Department of Emergency Medicine, Brooke Army Medical Center, 3841 Roger Brooke Drive, Fort Sam Houston, TX 78234

☐ **Abstract—Background: Palliative care is an essential component of emergency medicine, as many patients with terminal illness will present to the emergency department (ED) for symptomatic management at the end of life (EOL). Objective: This narrative review evaluates palliative care in the ED, with a focus on the literature behind management of EOL symptoms, especially dyspnea and cancer-related pain. Discussion: As the population ages, increasing numbers of patients present to the ED with severe EOL symptoms. An understanding of the role of palliative care in the ED is crucial to effectively communicating with these patients to determine their goals and provide medical care in line with their wishes. Beneficence, nonmaleficence, and patient autonomy are essential components of palliative care. Patients without medical decision-making capacity may have an advance directive, do not resuscitate or do not intubate order, or Portable Medical Orders for Life-Sustaining Treatment available to assist clinicians. Effective and empathetic communication with patients and families is vital to EOL care discussions. Two of the most common and distressing symptoms at the EOL are dyspnea and pain. The most effective treatment of EOL dyspnea is opioids, with literature showing little efficacy for other therapies. The most effective treatment for cancer-related pain is opioids, with expeditious pain control achievable with a rapid fentanyl titration. It is also important to address nausea, vomiting, and secretions, as these are common at the EOL. Conclusions: Emergency clinicians play a vital role in EOL patient care. Clear, empathetic communication and treatment of EOL symptoms are essential. Published by Elsevier Inc.**

☐ **Keywords—oncology; palliative; hospice; advanced directive; do not resuscitate and do not intubate orders; POLST; dyspnea; pain; analgesia**

INTRODUCTION

With advances in medical research, treatment, and technology, life expectancy across the world is continually increasing and so is the proportion of elderly among the population (1). According to the World Health Organization (WHO), the proportion of the world's population over 60 years of age will increase from 12% to 22% between 2015 to 2050 (1). As the population ages, the number of people living with end-stage cancer and other terminal illnesses continues to grow. During the next several decades, the burden of care for these patients will often fall on emergency physicians, as patients near the end of life (EOL) commonly present to the emergency department (ED) when outpatient symptom management fails. It is estimated that up to one-third of cancer patients visit the ED for symptom management during the last 2 weeks of life, and up to half of Medicare recipients visit the ED in the last month of their lives (2,3). Uncontrolled suffering is a significant concern for patients nearing the EOL. Along with alleviating EOL symptoms, emergency physicians must effectively and empathetically communicate with patients with terminal illnesses. This review will provide a summary of

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palliative care in the ED, with a focus on the literature behind management of EOL dyspnea and cancer-related pain.

METHODS

The authors searched PubMed and Google Scholar for articles using the keywords *palliative*, *end of life*, *hospice*, and *symptoms*. The search was conducted from PubMed and Google Scholar inception to October 12, 2019. PubMed yielded more than 500 articles. The first 200 articles in Google Scholar were also searched as recommended by Bramer et al. (4). Authors included case reports and series, retrospective and prospective studies, systematic reviews and meta-analyses, clinical guidelines, consensus statements, and other narrative reviews. The literature search was restricted to studies published in English. Emergency physicians with experience in critical appraisal of the literature reviewed all of the articles and decided which studies to include for the review by consensus, with a focus on emergency medicine–relevant articles pertaining to palliative medicine. When available, systematic reviews and meta-analyses were preferentially selected, followed sequentially by randomized controlled trials, prospective studies, retrospective studies, case reports, consensus statements, and other narrative reviews when alternate data were not available. A total of 89 resources were selected for inclusion in this review. Of these, 7 were meta-analyses, 7 were systematic reviews, 16 were randomized controlled trials, 12 were prospective studies, 3 were retrospective studies, 6 were descriptive studies, 15 were narrative reviews, 13 were expert consensus documents, 7 were textbook chapters, and 3 were editorials.

DISCUSSION

An understanding of palliative care is crucial for emergency physicians to appropriately provide care to patients nearing EOL. The WHO defines palliative care as "an approach that improves the quality of life of patients and their families facing the problem associated with life-threatening illness, through the prevention and relief of suffering by means of early identification and impeccable assessment and treatment of pain and other problems, physical, psychosocial and spiritual" (5). Other terms that are important to understand include *hospice car*e and c*omfort measures*. According to the American Cancer Society, hospice care is "a special kind of care that focuses on the quality of life for the people and their caregivers who are experiencing an advanced, life-limiting illness" (6). Hospice care, as a subset of palliative management, focuses on symptom relief for patients with a life expectancy of 6 months or less (7). Hospice care does not refer to a place but a care system. It is most commonly an outpatient service (70.3% of hospice patients), but patients may receive inpatient hospice care or be hospitalized at a hospice center (6,8). Comfort measures, as defined by the Joint Commission National Quality Core Measures Manual, refer to "medical treatment of a dying person where the dying process is permitted to occur while ensuring maximal comfort" (9). The goal of comfort measures is to provide symptom control near the EOL in a manner in line with the patient's wishes (7).

Aspects inherent in the field of palliative care form core foundations of the heart of medicine and medical ethics. Beneficence, nonmaleficence, and patient autonomy, while important in every patient encounter, are crucial during the interaction of patients nearing EOL. Beneficence can be thought of as maintaining the well-being of the patient first and foremost, and patient autonomy is the right of patients to make their own decisions regarding medical testing and treatment. These concepts may be challenging to uphold for the clinician when patients present at EOL without the cognitive function needed for medical decision-making (10). Many patients with terminal illnesses have previously documented their goals of care and wishes for medical treatment. These forms are often helpful to the emergency physician, as up to 70% of patients with terminal illness do not have decision-making capacity as they near EOL (11). There are three major written directives that help specify EOL medical therapies: advance directives, do not resuscitate (DNR) and do not intubate (DNI) orders, and Portable Medical Orders to Life-Sustaining Treatment (POLST).

Advance Directive

An advance directive is a document detailing the patient's future medical decisions and preferences in the event the patient is unable to communicate. It includes the living will, durable power of attorney for health care, and health care proxy. The living will is a legal document written and signed by the patient that specifies the patient's decisions for medical therapies. The durable power of attorney for health care is also a legal document signed by the patient that identifies the patient's choice for an individual to act as a medical decision-maker, provided the patient is unable to communicate his or her medical wishes. This individual is known as the health care proxy and acts on behalf of the patient to make medical decisions for the patient. If the patient has not identified a durable power of attorney for health care, the usual hierarchy for determining the health care proxy is the patient's spouse, adult children, parents, siblings, grandchildren, and close friends. If none of these forms are available and the patient's family or friends are unable to be contacted, the

physician should assume the patient wants life-sustaining treatment, and medical therapies (i.e., intubation, mechanical ventilation, and IV antibiotics) should be used as needed (7,12).

DNR and DNI Orders

The DNR is an order that states, in the event of cardiopulmonary arrest, the patient does not desire cardiopulmonary resuscitation (CPR) or advanced cardiac life support. This form does not apply to other medical decision-making and only applies in the instance the patient experiences cardiopulmonary arrest. A DNR order is different from a DNI order, which states that under no circumstances will the patient be intubated. A patient may have a DNR order without a DNI order, as the patient may wish to be intubated as part of a trial of critical care but does not wish to receive chest compressions if cardiopulmonary arrest occurs. Both of these forms are signed by the physician after discussion with the patient or health care proxy (13,14).

POLST Form

A POLST form is more specific than an advance directive. A POLST form is meant to act as a robust informed consent discussion between the patient or health care proxy and physician and is signed by both parties (15,16). POLST forms were first initiated in Oregon in 1995 and have become widespread since, with all 50 states and Washington, DC, currently carrying some version of a POLST form (17,18). In addition to specifying a patient's DNR or DNI status, a POLST form gives specific medical orders for interventions, such as noninvasive positive pressure ventilation, IV fluids, and antibiotics (Figure 1) (15–17). As seen in Figure 1, a POLST form clearly delineates DNR status, making it convenient for the health care provider to quickly determine code status in an emergency. A physical copy of the POLST form may be carried with the patient and is transferrable between different hospital systems (16).

There are multiple challenges that arise in the ED concerning POLST forms. As POLST forms can be detailed in specific therapies, emergency physicians may be unsure how aggressively to manage patients, especially in patients choosing options between full care and comfort care (16). In addition, emergency medical services crews or emergency physicians may be unaware when patients present to the ED with POLST forms previously completed documenting their goals of care. A retrospective study of patients presenting to the ED with previously completed POLST forms documented in the electronic health record found that prior to admission, emergency physicians only accessed the POLST form for 6.4% of patients (19).

While in certain circumstances it may be difficult to find or access previous documents detailing EOL wishes, it is crucial the physician inquire the patient or family and attempt to identify the patient's EOL wishes to provide care in accordance with the patient's goals. In addition, the clinician must clarify the various treatments listed on the POLST form with either the patient or his or her health care surrogate, as patients are able to change decisions on the POLST form or advance directive if their wishes change.

Effective Communication

An important component of palliative care is skillful communication with patients to gain trust, clarify goals of care, and determine what treatments the patient desires. Clarifying goals of care is essential to caring for patients nearing EOL. Unfortunately, there is often a large cognitive gap between the patient's perception of dying and the reality of the dying process. The duty of the physician is both to inform the patient and his or her family of the dying process and medical therapies available and elicit the patient's preferences in medical treatment. There are several methods for conveying empathy and effectively communicating with patients with a terminal disease. Empathy is essential during all interactions. A group of phrases that can be helpful in conveying empathy are the NURSE (naming, understanding, respecting, supporting, exploring) statements, shown in Figure 2 (7,20,21). These statements are geared towards acknowledging and responding to emotions from the patient and family and are invaluable in building a therapeutic alliance with the patient and family.

Another technique that can be useful is the ask-tell-ask technique (7,20). This approach assesses the patient's understanding of his or her medical situation, which allows the physician to appropriately communicate necessary information the patient will comprehend. The physician can then inquire "what do you think or feel about what I said?" or "what other concerns or questions do you have?" In addition, the physician can ask the patient or medical decision-maker to repeat the information conveyed to assess comprehension. The aim of these communication techniques is to build a therapeutic alliance with the patient and his or her family, convey to the patient that he or she has a voice in his or her medical care, and gain an understanding of the patient's wishes for his or her medical care.

Along with an understanding of EOL documents and effective communication techniques, an emergency physician must have an approach for conversations regarding goals of care. A guideline to an EOL care discussion is

HIPAA PERMITS DISCLOSURE OF POLST ORDERS TO HEALTH CARE PROVIDERS AS NECESSARY FOR TREATMENT
SEND FORM WITH PATIENT WHENEVER TRANSFERRED OR DISCHARGED

Medical Record # (Optional)

National POLST Form: A Portable Medical Order

Health care providers should complete this form only after a conversation with their patient or the patient's representative. The POLST decision-making process is for patients who are at risk for a life-threatening clinical event because they have a serious life-limiting medical condition, which may include advanced frailty (www.polst.org/guidance-appropriate-patients-pdf).

Patient Information. **Having a POLST form is always voluntary.**

This is a medical order, not an advance directive. For information about POLST and to understand this document, visit: www.polst.org/form

Patient First Name: _____

Middle Name/Initial: _____ Preferred name: _____

Last Name: _____ Suffix (Jr, Sr, etc): _____

DOB (mm/dd/yyyy): ____/____/_____ State where form was completed: _____

Gender: ☐ M ☐ F ☐ X Social Security Number's last 4 digits (optional): xxx-xx-___ ___ ___ ___

A. Cardiopulmonary Resuscitation Orders. Follow these orders if patient has no pulse and is not breathing.

Pick 1

☐ **YES CPR: Attempt Resuscitation, including mechanical ventilation, defibrillation and cardioversion.** (Requires choosing Full Treatments in Section B)

☐ **NO CPR: Do Not Attempt Resuscitation.** (May choose any option in Section B)

B. Initial Treatment Orders. Follow these orders if patient has a pulse and/or is breathing.

Reassess and discuss interventions with patient or patient representative regularly to ensure treatments are meeting patient's care goals. Consider a time-trial of interventions based on goals and specific outcomes.

Pick 1

☐ **Full Treatments (required if choose CPR in Section A).** Goal: Attempt to sustain life by all medically effective means. Provide appropriate medical and surgical treatments as indicated to attempt to prolong life, including intensive care.

☐ **Selective Treatments.** Goal: Attempt to restore function while avoiding intensive care and resuscitation efforts (ventilator, defibrillation and cardioversion). May use non-invasive positive airway pressure, antibiotics and IV fluids as indicated. Avoid intensive care. Transfer to hospital if treatment needs cannot be met in current location.

☐ **Comfort-focused Treatments.** Goal: Maximize comfort through symptom management; allow natural death. Use oxygen, suction and manual treatment of airway obstruction as needed for comfort. Avoid treatments listed in full or select treatments unless consistent with comfort goal. Transfer to hospital **only** if comfort cannot be achieved in current setting.

C. Additional Orders or Instructions. These orders are in addition to those above (e.g., blood products, dialysis).
[EMS protocols may limit emergency responder ability to act on orders in this section.]

D. Medically Assisted Nutrition (Offer food by mouth if desired by patient, safe and tolerated)

Pick 1

☐ Provide feeding through new or existing surgically-placed tubes ☐ No artificial means of nutrition desired

☐ Trial period for artificial nutrition but no surgically-placed tubes ☐ Discussed but no decision made (standard of care provided)

E. SIGNATURE: Patient or Patient Representative (eSigned documents are valid)

I understand this form is voluntary. I have discussed my treatment options and goals of care with my provider. If signing as the patient's representative, the treatments are consistent with the patient's known wishes and in their best interest.

✖ (required)

If other than patient, print full name: | **Authority:**

The most recently completed valid POLST form supersedes all previously completed POLST forms.

F. SIGNATURE: Health Care Provider (eSigned documents are valid) Verbal orders are acceptable with follow up signature.

I have discussed this order with the patient or his/her representative. The orders reflect the patient's known wishes, to the best of my knowledge. [Note: Only licensed health care providers authorized by law to sign POLST form in state where completed may sign this order]

✖ (required) | **Date** (mm/dd/yyyy): Required ___/___/___ | **Phone #** : (___)

Printed Full Name: | **License/Cert. #:**

Supervising physician signature: ☐ N/A | **License #:**

A copied, faxed or electronic version of this form is a legal and valid medical order. This form does not expire. 2019

Figure 1. Portable Medical Orders to Life-Sustaining Treatment (POLST) form. Permission for reuse obtained from www.polst.org.

NURSE mnemonic for responding to emotions
Naming o Name the emotion the patient seems to be experiencing
Understanding o Attempt to summarize what the patient is communicating, and ask the patient if your summary correctly reflects his/her emotions
Respecting o Acknowledge and respect the patient's emotions o Use phrases that praise the patient for coping with his/her illness
Supporting o Communicate that you care for the patient and are willing to help him/her through his/her illness
Exploring o Ask questions to clarify the patient's feelings and to show the patient you are invested in his/her care

Figure 2. NURSE (naming, understanding, respecting, supporting, exploring) statements.

depicted in Figure 3 (22). An initial step is to determine whether a patient has previously made decisions regarding EOL care documented in an advance directive or POLST form. If the patient has previously made decisions regarding EOL care, a discussion to verify the decisions in these documents is necessary. The next step is to address patient expectations and goals towards EOL care. This step is vital, as patients may not understand the reality of certain medical treatments or therapies. The patient should be asked what he or she understands about his or her medical condition and what expectations he or she has. Determining what is important to the patient in his or her remaining time is crucial to framing the discussion.

The provider should provide information as needed regarding EOL care, especially regarding resuscitation. For instance, when discussing a DNR order, a physician should not use the phrase "do you want us to do everything?"—which gives the patient the false impression that nothing will be done if he or she opts for no CPR. Instead, the choice of "having a natural death" or "passing away peacefully" should be presented as an alternative to full medical resuscitation. A 2013 randomized simulation experiment evaluated the effect of phrasing EOL interventions on surrogate decision-makers' choices and found that minor changes in physician wording and communication had a large impact on surrogate decision-maker decisions about CPR (25). Framing no CPR as the norm, rather than CPR being the norm, led to a 16% absolute reduction in the decision to be a full code (25). In addition, using the phrase "natural death" rather than "do not resuscitate" led to a 12% reduction in the decision to be a full code (25).

Steps for an EOL Care Discussion
Determine the patient's current status of advance directives o If the patient has an advance directive, verify the contents with the patient or healthcare proxy
Establish patient expectations/goals towards EOL care o "What is your current understanding of your health situation?" o "What goals do you have for your remaining time?" o "What is most important to you?"
Provide education towards EOL care o Tailor education to the patient's level of understanding o Avoid medical jargon; use phrases easy to understand o EOL care should not be depicted as an "all or nothing" option
Make joint decision with patient and family regarding EOL therapies o Ensure chosen therapies are in accordance with patient's stated wishes and goals for the remainder of his/her time
Document EOL care decisions o Convey EOL decisions to inpatient medical team or patient care team

Figure 3. Steps for an end of life (EOL) care discussion (22–24).

The next step is to formulate a plan with the patient and family. The provider should ensure the decisions made by the patient or health care proxy for EOL care are made in accordance with the patient's goals of care and how the patient wishes to spend the remainder of his or her time. The provider must convey empathy and respond appropriately to the patient's and family members' emotions during these encounters. The details of these discussions should be documented in the patient's chart and conveyed to the inpatient team.

Another technique for difficult EOL care discussions is the SPIKES (setup, perception, invitation, knowledge, empathize, summary) model (Figure 4) (20,26) This model may be helpful for breaking bad news, discussing unfavorable laboratory or imaging results, and for framing EOL discussions. It can be used prior to discussing advance directives to ensure the patient and family have a grasp of the overall medical condition of the patient.

EOL Symptom Management

There are four common trajectories for diseases, including sudden death, terminal illness, organ failure, and frailty (27). The most common terminal illness is malignancy, in which patients function well until the final months of life (27). It may be difficult to determine whether a patient with terminal illness is close to death. A common understanding of the EOL trajectory and EOL symptoms is helping to identifying patients presenting at the EOL. While every patient has a unique path towards death, there are certain factors that may be associated with shorter survival. One study found the most frequent symptoms during the last week of life (>50%) are anorexia, asthenia, dry mouth, confusion, and constipation (28). A prospective study on the dying process found certain EOL symptoms are correlated with time to death (29). In this study, the median time to death from the onset of death rattle, respiration with mandibular movement, cyanosis on extremities, and pulselessness of the radial artery was 23 h, 2.5 h, 1 h, and 1 h, respectively (29). Vital signs on presentation to the ED may also be a predictor of imminent death. One study examining prognostication of life expectancy in patients with advanced cancer found low systolic blood pressure, tachycardia, anorexia, and dyspnea were correlated with shorter survival (30).

When patients present to the ED near the EOL and death is imminent, the medical setting can be of particular importance for the patient and family. If possible, these patients should be moved to a quiet and private room. Monitors should be minimized and silenced. One strategy is to leave the pulse oximetry attached to monitor the waveform on the dying patient with the alarms turned

SPIKES model
Setup ○ Prepare yourself with the medical facts, including imaging and labs ○ Find a quiet place to have a discussion with the patient and/or family, where there will be minimal interruptions ○ Ensure everyone, including you, are seated
Perception ○ Ask the patient what he/she understands about his/her medical situation
Invitation ○ Find out how much information the patient wants to know
Knowledge ○ Use language the patient will understand; avoid medical jargon ○ Give a warning shot: "I am afraid I have some serious news to tell you." ○ If the patient's perception was inaccurate, review pertinent medical information ○ After giving the news, stay quiet and allow time for the patient and family to process
Empathize ○ Respond to any patient emotions ○ Utilize NURSE statements ○ Ask if the patient has any questions or concerns
Summary ○ Summarize the conveyed information and make a plan for the next step

Figure 4. SPIKES (setup, perception, invitation, knowledge, empathize, summary) model (20). NURSE = naming, understanding, respecting, supporting, exploring.

off, giving the medical team the ability to monitor the patient without significant intrusion (31). All efforts must be made to give the family a chance to spend the last moments with their loved one without fear of interruption or intrusion.

Patients nearing EOL often present to the ED after outpatient management has failed or symptoms have become uncontrolled. The WHO reviewed evidence of EOL symptoms and determined the following 11 symptoms to be the most common at EOL: anorexia, anxiety, constipation, delirium, depression, diarrhea, dyspnea, fatigue, nausea and vomiting, pain, and respiratory tract secretions (32). Two of the most distressing and difficult to treat EOL symptoms are dyspnea and pain. Patients nearing the EOL may be symptomatic from either complications of their terminal disease or other pathologic conditions. However, this review will not focus on the differential diagnosis of EOL dyspnea or pain but will instead focus on the ED management of these two symptoms.

Dyspnea

Dyspnea is one of the most distressing symptoms experienced by dying patients and is often disturbing and upsetting to caregivers and family members. In patients with terminal cancer, 70% to 80% experience dyspnea at some time during the last 6 weeks of life (33,34). There are multiple therapies that have been studied for management of EOL dyspnea, including opioids, oxygen, and noninvasive positive pressure ventilation (NIPPV). Contrary to the typical emergency management of patients with dyspnea and respiratory distress, tools such as endotracheal intubation and mechanical ventilation can lead to an extended intensive care unit course, increased suffering, and a prolonged dying process (12).

Opioids are the best studied therapy for EOL dyspnea and reduce chemoreceptor response to hypercapnia, anxiety, and the sensation of breathlessness (35,36). A Cochrane review of opioids for dyspnea encourages the use of oral and IV opioids for dyspnea in patients with terminal illness (37). This review identified nine trials involving the use of oral or parenteral opioids and found that oral and parenteral opioids possess a significant effect in the management of dyspnea. The studies used in this review were limited by small sample size, with the largest of the 9 studies consisting of only 19 patients. For patients who receive opioids, adverse effects such as constipation, nausea and vomiting, and drowsiness were more common (37). A systematic review and meta-analysis in 2012 examined therapies for EOL dyspnea (38). Three double-blinded randomized controlled crossover trials were included that evaluated opioid administration for alleviation of EOL dyspnea, finding a positive effect for opioid administration on dyspnea, with a weighted mean difference of −1.31 (95% confidence interval [CI] −2.49 to −0.18), with a more negative value favoring opioids vs. control (38–41).

Physicians may hesitate administering opioids due to the fear of hastening death. Literature does not support the notion that opioids trigger or quicken the dying process. A 2008 study examined the effect of hydromorphone on ventilation and intensity of dyspnea in palliative care patients (42). The authors found no significant decrease in oxygen saturation (SpO_2) or partial pressure of carbon dioxide ($PaCO_2$) after hydromorphone administration, and no patient had hydromorphone-induced respiratory depression, which was defined as significant decrease in SpO_2 or increase in $PaCO_2$. The first hydromorphone administration did lead to a decrease in both severity of dyspnea and respiratory rate (42). A 2012 meta-analysis did not find adverse events from management of dyspnea with opioids to include opioid-induced respiratory depression or somnolence (38). The safest method for opioid administration is to begin with a lower dose and escalate as needed for subjective improvement in shortness of breath. The dose of opioids for relief of EOL dyspnea is often lower than that commonly used for pain control. It is reasonable for emergency physicians to start with a dose of morphine 1 to 2 mg IV or hydromorphone 0.2 to 0.4 mg IV. Repeat doses can be given as necessary (12).

Literature does not support the routine use of oxygen for relief of EOL dyspnea. A 2012 meta-included 6 studies and 179 patients that examined the effect of oxygen on EOL dyspnea (40,43–47). The intervention was similar in five of these studies, with oxygen administered via nasal cannula (4–5 L/min) vs. air (40,43,45–47). This meta-analysis failed to show benefit of oxygen in relieving dyspnea, with a standardized mean difference of 0.3 (95% CI −1.06 to 0.47) (38).

Benzodiazepines are another potential therapy for EOL dyspnea. The literature is controversial on utility of benzodiazepines in alleviating EOL dyspnea. Two studies compared midazolam vs. morphine vs. a combination of the two drugs in treatment of dyspnea in cancer patients (48,49). In the first study, morphine appeared more effective for relieving dyspnea than midazolam at 24 h, but this result was not statistically significant. The authors concluded that the effect of morphine in alleviation of EOL dyspnea may be improved with the addition of midazolam (48). The second study found dyspnea was relieved by at least 50% in both the morphine and midazolam group (49). A Cochrane review of eight studies did not find any benefit of benzodiazepines in alleviation of dyspnea compared with placebo or opioids, and adverse events (drowsiness and somnolence) were increased (50). Benzodiazepines may be helpful in treating

symptoms commonly associated with EOL dyspnea, such as anxiety, but their use may lead to increased somnolence and sedation. Their current role in EOL dyspnea remains controversial.

NIPPV may be considered in patients presenting with EOL dyspnea. A randomized controlled trial attempted to assess the effectiveness of NIPPV vs. standard medical therapy in reducing intubation, improving survival, and reducing respiratory distress in patients > 75 years of age (51). This study consisted of 82 patients and found the rate of intubation (primary outcome) was decreased in the NIPPV group compared with the standard medical therapy group (7.3% vs. 63.4%). Authors found blood gas results, respiratory rate, and dyspnea improved significantly faster with NIPPV compared with standard medical therapy, although these were secondary outcomes. The authors concluded that NIPPV should be considered for patients with DNI status or those considered poor candidates for intubation (51). In a prospective study of 23 patients with solid malignancies presenting with acute respiratory failure, NIPPV was found to significantly improve the Borg dyspnea scale (used to rate difficulty of breathing from 0 (no difficulty breathing) to 10 (maximum difficulty breathing)) from 5.5 ± 1.2 to 2.3 ± 0.3 after 1 h (52). In addition, NIPPV improved the PaO_2/FiO_2 (fraction of inspired oxygen) ratio from 154 ± 48 to 187 ± 55 after 1 h (52). NIPPV can assist patients presenting with reversible causes of respiratory distress and may give the family and patient time to consider further goals of care. However, NIPPV can be uncomfortable for patients and can potentially increase suffering and prolong the death trajectory.

Distress Protocol

Godbout et al. described a "distress protocol" to induce transient sedation for terminally ill patients with lung cancer or chronic obstructive pulmonary disease (COPD) presenting with respiratory distress (53). This protocol combines an opioid, benzodiazepine, and muscarinic antagonist. In this study, patients received a combination of 5 mg midazolam, 10 mg morphine, and 0.4 mg scopolamine, all by subcutaneous route. All patients who received the protocol (96 patients with cancer and 85 patients with COPD) were adequately sedated within 30 min. Furthermore, this study found no difference in survival for those patients who received the protocol and those who did not, providing support that the therapies used in this protocol do not expedite death. This protocol can be repeated in 15 min as needed for appropriate sedation.

Pain

Patients nearing EOL, especially those living with end-stage cancer, can experience acute pain exacerbation. Approximately 50% of patients experience significant pain at EOL (54). Three common types of pain include nociceptive, neuropathic, and bone pain (Table 1) (55,56). Nociceptive pain occurs due to stretch or compression of organs, neuropathic pain presents with burning or lancinating pain from nerve injury, and bone pain with deep and boring pain from bone metastasis or pathologic fracture. Much of the literature on management of EOL pain is based on the cancer population.

Prior to engaging in treatment of these pain exacerbations, the emergency physician must accurately gauge the

Table 1. Types of Pain

Type	Pathophysiology	Characteristics	Treatment
Nociceptive	Caused by stretch or compression of somatic or visceral nociceptive pain receptors Somatic pain receptors are highly myelinated, rapidly transmit painful sensations Visceral receptors are less myelinated, slower transmission of pain	Sharp and stabbing, well localized (somatic pain receptors) Dull, aching, or cramping Poorly localized (visceral pain receptors)	First line for severe pain is opioids First line for mild to moderate pain is acetaminophen or NSAIDs Consider adjuvant pain medications as needed (e.g., ketamine)
Neuropathic	Damage to nerves from multiple mechanisms (e.g., tumor invasion, chemotherapy, microvascular injury, infection)	Numbness, tingling, burning sensation	Antidepressants or anticonvulsants
Bone pain	Tumor invasion or metastasis to bone Pathologic bone fractures	Deep, boring pain over affected bones	First line for mild to moderate bone pain is NSAIDs Severe pain will likely require opioids Add adjuvant pain medications as needed

NSAID = nonsteroidal anti-inflammatory drug.

patient's degree of pain. There are multiple modalities for pain assessment. Commonly used scales include visual analog scale, numerical rating scale, Wong-Baker FACES scale, and the verbal rating scale (57). These scales use a spectrum of "no pain" to "worst pain" to measure degree of pain. No pain scale has been shown to be superior to others (57). It is key that once a tool is chosen for the patient, the same tool is used for the duration of the encounter to adequately measure analgesic effect. The physician should ensure patient expectations are established early and convey that it may be unlikely that the patient's pain will be completely alleviated to a score of "0" or "no pain." Rather, the goal of the encounter should be to achieve an adequate level of analgesia for the patient with improved comfort.

Unfortunately, verbal communication is not feasible for all patients presenting to the ED. For patients with severe dementia, the Pain Assessment in Advanced Dementia scale may be used (58). This scale takes into account the patient's breathing, vocalization, facial expression, body language, and consolability to rate a patient's pain as mild, moderate, or severe (Figure 5). Another useful scale in nonverbal patients is the Critical Care Pain Observation Tool (59). This scale can be used in intubated patients and considers compliance with the ventilator (if intubated), vocalization (if not intubated), facial expression, body movements, and muscle tension to grade a patient's pain as either minimal pain or an unacceptable level of pain.

Patients with mild to moderate pain may be treated first with oral acetaminophen or a nonsteroidal anti-inflammatory drug (NSAID). For patients presenting to the ED with severe pain, the oral or rectal routes are not ideal, as these routes have a longer time to peak effect that limits titration and rapid pain control (60). Patients in the ED with severe pain should receive IV administration of pain medications.

Opioids

Opioids are considered first-line therapy for patients with acute severe pain and are most efficacious for nociceptive pain. Opioids act by binding to specific receptors found in both the peripheral and central nervous system. The receptor thought to control the analgesic response is the mu receptor (56,60).

The most common parenteral opioids used in the ED include morphine, hydromorphone, and fentanyl. Profiles of each of these drugs are highlighted in Table 2 (56).

Patients with cancer will present at various stages through the course of their disease, and many will be taking opioids as part of their outpatient pain regimen. Patients may be considered opioid-tolerant if they are consistently taking at least 60 mg oral morphine (or

Observation	**0**	**1**	**2**
Breathing Independent of vocalization	-Normal	-Occasional labored breathing -Short period of hyperventilation	-Noisy and labored breathing -Long period of hyperventilation -Cheyne-Stokes respirations
Negative vocalization	-None	-Occasional groan -Low-level speech with a negative quality	-Repeated troubled calling out -Load groaning -crying
Facial expression	-Smiling or inexpressive	-sad -frightened -frown	-Facial grimacing
Body language	-relaxed	-Tense -Distressed pacing -Fidgeting	-Rigid -Fists clenched -Knees pulled up -Pulling or pushing away -Striking out
Consolability	-No need to console	-Distracted or reassured by voice or touch	-Unable to console, distract, or reassure

Figure 5. Pain Assessment in Advanced Dementia scale.

Table 2. Pain Profiles of Fentanyl, Morphine, and Hydromorphone

Drug (Parenteral)	Sample Initial Dose (Opioid-Naïve Patients)	Onset (min)	Peak Effect (min)	Duration of Effect (h)	Comments
Fentanyl	50–100 μg every 30–60 min (1.0 μg/kg)	<1	2–5	0.5–1	Duration of effect increases after repeated use; less cardiovascular depression than morphine Minimal renal clearance High doses reported to cause rigidity
Morphine	4 mg IV every 2 h (0.1 mg/kg)	1–2	3–5	1–2	Avoid or use reduced dose and frequency in patients with impaired renal function May cause itching secondary to histamine release May lead to hypotension
Hydromorphone	0.4–1 mg IV every 2–4 h (0.015 mg/kg)	3–5	7–10	2–4	Preferred over morphine in patients with renal dysfunction Less pruritus compared with morphine

equivalent dosing) per day (56). Figure 6 displays opioid conversions, which are based on oral morphine equivalents (OMEs) (61–63). All other patients should be considered opioid-naïve. For patients with severe cancer pain who are opioid-naïve, initial starting doses of opioid similar to patients presenting with severe noncancer pain can be used (Table 1).

Determining the initial dose of opioid in opioid-tolerant patients can be challenging. A common approach to determining the initial dose of pain medication for cancer patients presenting with a pain crisis depends on calculating their 24-h OME (60,64–66). The initial breakthrough dose is 10% to 15% of the daily OME, which can be titrated upward as required for adequate pain control. When switching between different opioids, the calculated conversion dose of the new opioid should be reduced by 25% to 50% because tolerance to one opioid may not equal tolerance to a different opioid. If the provider does not want to switch the patient from his or her outpatient opioid regimen, the baseline dose should be increased by 50% to 100%

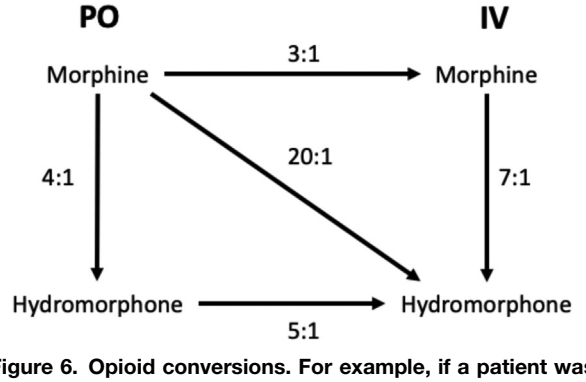

Figure 6. Opioid conversions. For example, if a patient was taking 100 mg of oral morphine per day, this would be equal to 33 mg IV morphine, and 5 mg of IV hydromorphone. PO = per os.

for patients presenting with moderate to severe cancer pain. The recommended frequency of dose escalation depends on the specific opioids being used. Morphine and hydromorphone can be escalated every 2 h, and fentanyl dosing can be increased more rapidly (60,64–66).

A 2003 study examined rapid dose escalation of IV fentanyl for severe cancer pain and achieved successful pain control in all 18 cancer patients included in the study (67). The average oral morphine consumption in the included patients was 276 mg (outpatient regimen). The average time to pain control in these patients was 11 min, with an average dose of fentanyl required for adequate pain control of 214 μg. Although this is a small cohort, rapid dosing and titration of fentanyl has several advantages. Fentanyl achieves peak effect in < 5 min, which allows for rapid titration, is less likely to cause hypotension, and has minimal renal clearance (56).

Morphine may also achieve adequate analgesia in the cancer patient with severe pain but does not work as rapidly as fentanyl. When an IV morphine titration is performed on patients who are opioid-tolerant, up to 215 min may be required for adequate pain control (68). A rapid fentanyl titration model may achieve pain control more quickly, providing patient comfort. An adapted model of the rapid fentanyl dose titration is shown in Figure 7. The goal of the rapid fentanyl titration model is to rapidly alleviate severe pain. Once the patient's pain is adequately controlled, the clinician can switch to a longer-acting alternative, such as IV hydromorphone or morphine as needed.

Nonopioid Analgesia

Nonsteroidal anti-inflammatory drugs. The WHO recommends NSAIDs as an initial pain medication for patients with mild to moderate cancer pain, especially bone pain (Table 3) (69). Bone pain is associated with prostaglandin

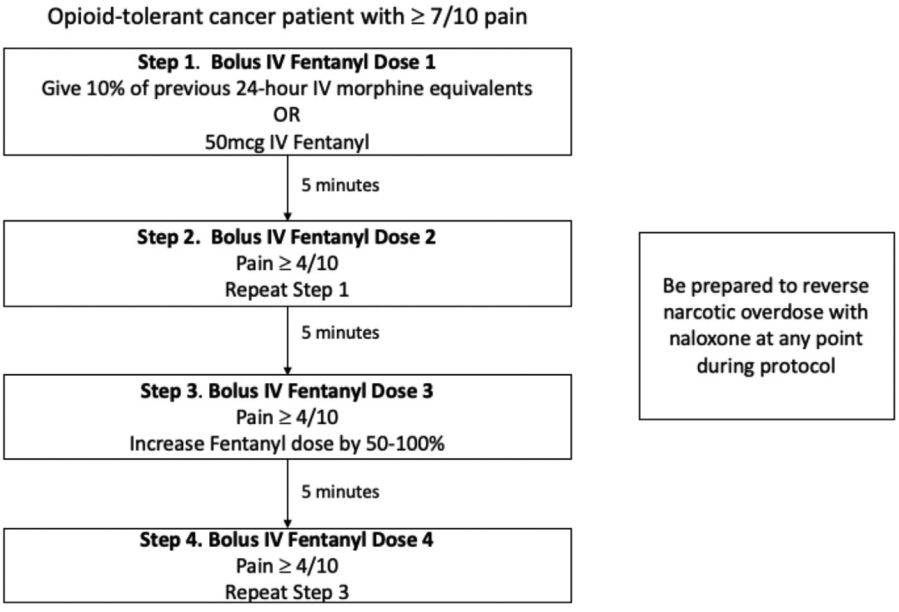

Figure 7. Rapid fentanyl dose titration model.

Table 3. Nonopioid Analgesic Medications

Medication	Mechanism	Dosing	Comments
Nonsteroidal anti-inflammatory drugs	Decrease prostaglandin activity	Ibuprofen 400–800 mg PO Naproxen 250–500 mg PO Toradol 10–30 mg IV or 30–60 mg IM	Associated with increased risk of gastrointestinal bleeding Relatively contraindicated in renal, hepatic, cardiac disease/failure
Acetaminophen	Unclear mechanism of action	650 mg or 1000 mg PO; 1000 mg IV; can also be given PR	Contraindicated in liver failure
Ketamine	NMDA receptor antagonist	0.1–0.3 mg/kg IV	Multiple adverse effects including emesis, hypersalivation, psychiatric distress, respiratory depression (if pushed rapidly), and dissociation May be beneficial in opioid-refractory pain
Corticosteroids	Anti-inflammatory mechanism	Dexamethasone 0.3–0.6 mg/kg up to 10 mg PO or IV Methylprednisolone 16 mg PO Prednisone 40–60 mg PO	No one steroid shown to be beneficial over another
Antidepressants	Selective serotonin reuptake inhibitors or serotonin-norepinephrine reuptake inhibitors Tricyclic antidepressant (amitriptyline)	Venlafaxine 15–100 mg PO Amitriptyline 25–100 mg PO	Used for treatment of neuropathic pain Many adverse effects including antimuscarinic effects, sodium channel blockade, antihistamine effects, α-1 receptor blockade Exercise extreme caution prior to prescribing outpatient
Anticonvulsants	Various mechanisms of action	Levetiracetam 1500 mg PO Pregabalin 75–300 mg PO Gabapentin 100–1200 mg PO Lamotrigine 150 mg PO	Used for neuropathic pain Many adverse effects including mood and behavior changes, Stevens-Johnson syndrome/toxic epidermal necrolysis, leukopenia, nausea or vomiting, and others Exercise extreme caution prior to prescribing outpatient

IM = intramuscular; NMDA = N-methyl-D-aspartate; PO = per os; PR = per rectum.

activity, which is reduced by NSAIDs. Up to 80% of patients will have a response to an NSAID (70). A systematic review in 2012 examined the addition of NSAIDs (both ketorolac and ibuprofen) to opioids in patients with cancer pain (71). In the review, 5 of 7 studies showed an additive effect of NSAIDs when combined with opioids, either in reducing the opioid dose (2 studies) or leading to improved pain control (3 studies) (72–76). NSAIDs included in these studies were diclofenac, ibuprofen, ketorolac, and dipyrone. A more recent systematic review in 2019 found 30 studies that evaluated the use of NSAIDs in cancer pain management (77). These authors concluded that the literature evaluating NSAIDs for cancer pain is poor, and there is no high-quality evidence regarding the effectiveness of NSAIDs in reducing cancer pain (77). However, the results of these studies suggested that NSAIDs are more effective than placebo in reducing pain intensity for patients suffering from cancer pain. This review also found that patients receiving NSAIDs in addition to opioids had decreased opioid dosage and greater pain relief compared with placebo. Review of the literature found no specific NSAID was superior to another.

Options for NSAIDs include ibuprofen 400 to 800 mg by mouth, naproxen 250 to 500 mg by mouth, or ketorolac 10 to 30 mg IV or 30 to 60 mg intramuscularly. NSAIDs are associated with risks of gastrointestinal bleeding and are relatively contraindicated in patients with renal, hepatic, and cardiac failure (71,77).

Acetaminophen. In addition to NSAIDs, the WHO cancer pain ladder recommends starting with acetaminophen for mild to moderate cancer pain (Table 3) (69). There is a paucity of literature evaluating acetaminophen for cancer pain. Nabal et al. found only marginal improvement in pain with the addition of acetaminophen to opioids reported in one of five trials (71). Doses of acetaminophen in these studies ranged from 3 to 5 g/day, with the positive study using the highest acetaminophen dose (5 g/day) (78). Acetaminophen should be used with caution in patients with liver failure (71). Acetaminophen can be dosed at 650 mg every 4 to 6 h or 1000 mg every 6 h by mouth. Acetaminophen can also be given IV up to 1000 mg every 6 h. The maximum daily recommended dose is 4 g. When using 4 g of acetaminophen or more per day, the clinician must consider the potential risk of hepatotoxicity.

Ketamine. Ketamine is an N-methyl-D-aspartate receptor antagonist (Table 3). A 2017 Cochrane review found current evidence is insufficient to assess the risks and benefits of ketamine as an adjunct to opioids for the relief of cancer pain (79). The evidence found in this review was low quality. The authors also concluded that rapid dose escalation of ketamine has unclear clinical benefit but is associated with significant adverse effects (79). A systematic review in 2013 identified five randomized double-blind controlled trials examining the use of ketamine for cancer pain (80). Unfortunately, the included studies were small and varied significantly concerning route of administration, dosing, and patient populations. The authors found that ketamine inconsistently improved pain control compared with placebo and concluded that there is no evidence that ketamine is superior to other therapies for treatment of cancer pain. Although data for ketamine in patients with cancer pain are poor, ketamine remains a viable option for patients with severe cancer pain that is refractory to opioids.

When administering ketamine, a clinician must be aware of adverse effects, including emesis, hypersalivation, psychiatric distress, and respiratory depression (79,80). Ketamine should not be used in patients with bipolar disorder, schizophrenia, and psychosis (79,80). The analgesic dose of ketamine is 0.1 to 0.3 mg/kg IV, which is often given in a 250 mL bag of normal saline over 10-15 min (81,82).

Corticosteroids. Corticosteroids may act an as anti-inflammatory agent to modulate the pain response in cancer patients (Table 3). Corticosteroids for cancer pain were assessed in a 2013 systematic review consisting of four studies, which yielded mixed results (83). Only one study found a reduction in pain intensity in addition to lower analgesic consumption (84). This study examined methylprednisolone 16 mg twice daily vs. placebo and found pain intensity, assessed by visual analog scale (0–100), was lower in the steroid group compared with placebo group (mean $\pm$ standard deviation 36.8 $\pm$ 14 vs. 50.1 $\pm$ 15; $p < 0.01$) (84). The systematic review concluded that corticosteroids may have a moderate analgesic effect in cancer patients, with the evidence graded as very low (83). Options include dexamethasone 0.6 mg/kg per os (PO) or IV, methylprednisolone 16 mg PO, or prednisone 40 to 60 mg PO.

Neuropathic Pain

Neuropathic pain may be difficult to treat with standard pain medications, such as NSAIDs or acetaminophen. Neuropathic pain is more commonly reported as numbness, tingling, hyperalgesia, or allodynia (60). Options for treatment of neuropathic pain include amitriptyline, venlafaxine, levetiracetam, pregabalin, gabapentin, or lamotrigine (Table 3). One systematic review found that antidepressants, anticonvulsants, opioids, or other adjuvant analgesics had a beneficial effect on patients with neuropathic cancer pain (85). Medications used in these studies include amitriptyline (15–100 mg PO), venlafaxine

(18.75 mg PO), levetiracetam (1500 mg PO twice daily), pregabalin (75–300 mg PO twice daily), gabapentin (100–1200 mg PO), and lamotrigine (150 mg twice daily). A Cochrane review of 61 trials examining antidepressants for neuropathic pain found that tricyclic antidepressants are effective in relief of neuropathic pain, with a number needed to treat (NNT) of 3.6 (86). Venlafaxine was found to have an NNT of 3.1 (86). However, this Cochrane review focused solely on patients with neuropathic pain and did not include patients suffering from neuropathic cancer pain.

The clinician must consider adverse effects of these agents before use. Tricyclic antidepressants have many potential adverse effects due to antimuscarinic effects, sodium channel blockade, antihistamine effects, and α-1 receptor blockade, and can be rapidly fatal in overdose (60,85,86). Adverse effects of agents for neuropathic pain greatly limit their use in the ED, and patients should not be discharged home on antineuropathic agents unless they have confirmed follow-up to monitor for any toxic or adverse effects. Pregabalin has a shorter up-titration period compared with gabapentin and can be effective in 1 to 2 days compared with 9 days for gabapentin (87).

EOL Nausea

Nausea in patients presenting near the EOL is complex and may be difficult to manage. The medulla receives inputs from the cerebral cortex, vestibular system of the inner ear, and sensory and visceral organs. Another major apparatus in the nausea response is the chemoreceptor trigger zone (CTZ). The CTZ is located in the fourth ventricle and secretes multiple neurotransmitters, including serotonin, dopamine, histamine, and acetylcholine to the vomiting center, initiating the vomiting reflex (55).

Many of the therapies aimed at relief of nausea and vomiting target the CTZ (Table 4). Ondansetron 4 to 8 mg IV or PO is a first-line therapy, especially for nausea and vomiting from chemotherapy (55,88). Metoclopramide 5 to 15 mg PO or IV every 8 h, haloperidol 2 to 5 mg IV every 8 h, chlorpromazine 10 to 25 mg PO or 25 mg IV, and prochlorperazine 5 to 10 mg PO or IV every 4 h are potential treatments. Treatments for vestibular causes of nausea and vomiting can be managed with an antihistamine agent, such as diphenhydramine, meclizine, or scopolamine, an anticholinergic medication. If a patient has increased intracranial pressure from intracranial masses, dexamethasone 10 mg PO or IV is an effective treatment for nausea and vomiting. A final medication class used for motion-induced nausea and vomiting includes benzodiazepines (55,88). Benzodiazepines are $GABA_A$ modulators, which increase the activity of GABA (88). Benzodiazepines that can be used to treat refractory nausea or vomiting include lorazepam, diazepam, or midazolam.

Table 4. Medications for End of Life Nausea and Vomiting

Medication	Mechanism of Action	Dosing	Comments
Ondansetron	Serotonin 5-HT_3 receptor antagonist	4–8 mg IV or PO	Standard first-line therapy for nausea
Metoclopramide	D_2 receptor antagonist, mixed serotonin 5-HT_3 and 5-HT_4 receptor antagonist	5–15 mg IV or PO	Promotility effect May provide analgesia Most common adverse effect is extrapyramidal symptoms
Haloperidol	Butyrophenone antipsychotic, mixed dopamine, and serotonin receptor activity	2–5 mg IV or IM, 5–10 mg PO	Most common adverse effect is extrapyramidal symptoms May alleviate pain and anxiety
Prochlorperazine	D_2 receptor antagonist	10 mg IV or PO	May provide analgesia Most common adverse effect is extrapyramidal symptoms
Chlorpromazine	Phenothiazine, first-generation antipsychotic	10–25 mg PO or 25 mg IV	Can result in extrapyramidal symptoms
Diphenhydramine or Meclizine	Antihistaminergic and anticholinergic	Diphenhydramine 25–50 mg PO, IM, or IV Meclizine 25 mg PO	May treat vestibular causes of nausea and vomiting May result in anticholinergic adverse effects
Scopolamine	Anticholinergic	0.4–0.8 mg PO, or 1 transdermal patch	Most often given as transdermal patch
Lorazepam	Benzodiazepine, increases frequency of GABA channel opening	0.5–2 mg IV or IM, 1–2 mg PO	May be helpful for nausea refractory to other therapies
Dexamethasone	Corticosteroid, anti-inflammatory	10 mg IV, IM, or PO	May alleviate nausea from increased ICP

CTZ = chemoreceptor trigger zone; ICP = intracranial pressure; IM = intramuscular, PO = per os.

Table 5. Treatment of End of Life Secretions

Medication	Mechanism of Action	Dosing
Glycopyrrolate	Anticholinergic	0.2 mg IV or 1 mg PO
Hyoscyamine	Anticholinergic	0.125 mg PO
Atropine	Anticholinergic	0.1 mg IV or 1% ophthalmic drops given as 1–2 drops sublingually

PO = per os.

Terminal Secretions

Near the EOL, secretions may gather in the airway, leading to noisy breathing, also known as the "death rattle." This noisy breathing is often upsetting to the patient's loved ones. The death rattle typically signifies that death is only hours away (28). The death rattle occurs in up to 92% of patients who are dying (89). Despite the paucity of literature for medical management of the death rattle, anticholinergic medications are commonly used. These agents include glycopyrrolate, hyoscyamine, and atropine (Table 5) (56). A 2008 Cochrane review of randomized controlled trials of treatments for the death rattle only found one study that met inclusion criteria, which was a randomized placebo-controlled trial of the use of hyoscine hydrobromide in patients with the death rattle (89,90). The authors of the Cochrane review concluded that there is currently no evidence to show that any intervention is superior to placebo (89).

CONCLUSIONS

Patients presenting to the ED with EOL symptoms are likely to become more common. Emergency physicians should seek to clarify goals of care and determine whether a patient has previously documented their EOL wishes for medical interventions. If the patient is unable to communicate, the physician should attempt to determine the health care proxy. For patients presenting with EOL dyspnea, opioids are the mainstay of treatment with little evidence to support the routine use of oxygen, benzodiazepines, or NIPPV. NIPPV is controversial, as it can prolong life at the cost of increasing patient discomfort. The most effective therapy for cancer-related pain is opioids. For rapid alleviation of severe pain, emergency physicians may use a fentanyl rapid dose titration model. There is no literature supporting the notion that opioids hasten death at EOL. Nausea, vomiting, and terminal secretions are other common conditions at the EOL. There is no single treatment for EOL nausea, vomiting, or terminal secretions.

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ARTICLE SUMMARY

1. Why is this topic important?

Palliative care is an important aspect of emergency medicine, with more terminally ill patients presenting to the emergency department (ED).

2. What does this review attempt to show?

This narrative review focuses on management of end of life (EOL) symptoms in the ED.

3. What are the key findings?

An understanding of palliative care is an important component of emergency medicine. Empathetic communication with patients and their families provides the foundation for effective EOL care. Assessment for the presence of advance directives, do not resuscitate and do not intubate orders, and Portable Medical Orders for Life-Sustaining Treatment is vital in patients without medical decision-making capacity. Common distressing EOL symptoms include dyspnea, pain, nausea and vomiting, and terminal secretions.

4. How is patient care impacted?

Emergency clinicians possess an integral role in the management of EOL symptoms and should provide clear, empathetic communication to patients and families when discussing EOL issues.