

# End-of-Life Care: Managing Common Symptoms

ROSS H. ALBERT, MD, PhD, *Hartford Hospital, Hartford, Connecticut*

Physicians should be proficient at managing symptoms as patients progress through the dying process. When possible, proactive regimens that prevent symptoms should be used, because it is generally easier to prevent than to treat an acute symptom. As swallowing function diminishes, medications are typically administered sublingually, transdermally, or via rectal suppository. Opiates are the medication of choice for the control of pain and dyspnea, which are common symptoms in the dying process. Delirium and agitation may be caused by reversible etiologies, which should be identified and treated when feasible. When medications are required, haloperidol and risperidone are effective options for delirium. Nausea and vomiting should be treated with medications targeting the etiology. Constipation may be caused by low oral intake or opiate use. Preventive regimens to avoid constipation should include a stimulant laxative with a stool softener. Oropharyngeal secretions may lead to noisy breathing, sometimes referred to as a death rattle, which is common at the end of life. Providing anticipatory guidance helps families and caregivers normalize this symptom. Anticholinergic medications can modestly help reduce these secretions. Effective symptom control in end-of-life care can allow patients to progress through the dying process in a safe, dignified, and comfortable manner. (*Am Fam Physician*. 2017;95(6):356-361. Copyright © 2017 American Academy of Family Physicians.)

**CME** This clinical content conforms to AAFP criteria for continuing medical education (CME). See CME Quiz Questions on page 353.

Author disclosure: No relevant financial affiliations.

► **Patient information:** A handout on this topic is available at <http://www.aafp.org/afp/2009/0615/p1059-s1.html>.

In its report “Dying in America,” the Institute of Medicine stresses that “all clinicians across disciplines and specialties who care for people with advanced serious illness should be competent in basic palliative care, including communication skills, interprofessional collaboration, and symptom management.”<sup>1</sup> As clinicians assist patients and families through the course of disease, eventually, the care will focus on symptom management in the last weeks and days of life. Outside of the hospital, these care plans are directed by primary care physicians and subspecialists who have been managing patients’ primary illness, often without the aid of a palliative medicine-trained physician. Therefore, it is imperative that clinicians understand how to help these patients achieve symptom relief. This review focuses on the outpatient management of common symptoms in persons at the end of life, whether in the home, assisted living facility, or nursing home environment.

## General Principles

Clinicians should follow certain guiding principles when prescribing medications for symptom management at the end of life. Medications should be used to treat the

primary etiology of a symptom. For example, if a patient is anxious because of shortness of breath, treatment should focus on the dyspnea to alleviate the primary symptom and then the resulting anxiety.

Medications should generally start at lower dosages before titrating to the desired effect. The dosing should initially be as needed and then transitioned to a standing dosage or long-acting medication for symptom management. When possible, proactive regimens that prevent symptoms should be used, because it is generally easier to prevent than to treat an acute symptom.

Because disrupted swallowing function and changes in the level of wakefulness can affect patients’ ability to swallow pills, medications must be provided in formulations that are safe and feasible for administration. Concentrated sublingual medications, dissolvable tablets, transdermal patches, creams or gels, and rectal suppositories can be given to patients with impaired swallowing and decreased responsiveness. Less common formulations may be obtained at local compounding pharmacies and hospice pharmacies. If sublingual tablets are used, mucous membranes must remain moist through careful oral care to allow for optimal absorption.

## SORT: KEY RECOMMENDATIONS FOR PRACTICE

<i>Clinical recommendation</i>	<i>Evidence rating</i>	<i>References</i>
Opiates should be used to treat dyspnea in end-of-life care.	B	3-5
Haloperidol and risperidone (Risperdal) are effective in treating delirium in end-of-life care.	C	17
Corticosteroids should be used in the management of bowel obstruction caused by malignancy. Octreotide (Sandostatin) has been shown to have limited benefit.	B	28, 29
Hyoscyamine (Levsin) or atropine ophthalmic drops can be used to treat excessive oropharyngeal secretions, although evidence supporting their use is limited.	C	33, 34

A = consistent, good-quality patient-oriented evidence; B = inconsistent or limited-quality patient-oriented evidence; C = consensus, disease-oriented evidence, usual practice, expert opinion, or case series. For information about the SORT evidence rating system, go to <http://www.aafp.org/afpsort>.

## Pain

Pain is a common symptom occurring in approximately 50% of persons in the last month of life.<sup>2</sup> It is important to recognize a patient's total pain, which includes not only physical symptoms but also the psychological, social, and spiritual components of distress. Although regulations and scrutiny surrounding the use of opiates for acute and chronic pain have increased, opiates remain the medication of choice for treating physical pain in patients at the end of life (Table 1).<sup>3-6</sup> A review of pain management at the end of life was recently published in *American Family Physician* and can provide additional information on this topic.<sup>7</sup>

## Dyspnea

Although dyspnea often occurs in patients with end-stage pulmonary and cardiac disease, it is also regularly observed in patients with cancer, cerebrovascular disease, or dementia.<sup>8-11</sup> Dyspnea can be caused by a number of different mechanisms, including aspiration pneumonitis or pneumonia, airway hyperreactivity, pulmonary edema, pleural effusions, and deconditioning. Measuring and quantifying dyspnea in patients with decreased responsiveness at the end of life can be challenging because most dyspnea scales require the patient to report symptoms. The Respiratory Distress Observation

Scale ([http://homecareinformation.net/handouts/hen/Respiratory\\_Distress\\_Observation\\_Scale.pdf](http://homecareinformation.net/handouts/hen/Respiratory_Distress_Observation_Scale.pdf)) is an eight-variable tool yielding a score of 0 (no dyspnea) to 16 (most dyspnea) based on observers' clinical assessments, and has been studied in the care of patients at the end of life.<sup>12</sup> Tachypnea, increased difficulty breathing, restlessness, and grunting are clinical signs of dyspnea, regardless of a patient's measured oxygen saturation.

Opiates are the medication of choice for the management of breathlessness in end-of-life care.<sup>3-5</sup> When administered at appropriate doses, opiates do not reduce or compromise respiratory status and do not hasten dying.<sup>13,14</sup> Opiates help to reduce the sense of air hunger in patients with dyspnea. The use of opiates for palliative therapy in advanced pulmonary disease is supported by clinical guidelines from the American Thoracic Society.<sup>6</sup>

Opiates should be selected and administered based on patients' comorbidities, previous opiate exposure, and the ease of administration. Opiates should be started at low doses with short dosing intervals and first provided on an as-needed basis. Common initial dosing regimens for dyspnea are shown in Table 1.<sup>3-6</sup> This will allow for rapid titration, which prescribers can use to calculate the total daily dosage needed to control symptoms. This total dosage can be transitioned to long-acting

**Table 1. Initial Opiate Dosages for Moderate to Severe Dyspnea or Pain in Opioid-Naive Patients During End-of-Life Care**

<i>Medication</i>	<i>Oral dose</i>	<i>Intravenous or subcutaneous dose</i>	<i>Initial dosing frequency</i>
Fentanyl	NA	25 to 100 mcg	Every 2 to 3 hours
Hydromorphone (Dilaudid)	2 to 4 mg	0.5 to 2 mg	Every 3 to 4 hours
Morphine	2.5 to 10 mg	2 to 10 mg	Every 3 to 4 hours
Oxycodone	2.5 to 10 mg	NA	Every 3 to 4 hours

NOTE: Long-acting opiates, such as transdermal fentanyl, oxycodone extended release, and morphine extended release, are not recommended for the initial titration of opiates for pain or dyspnea.

NA = not available.

Information from references 3 through 6.

## End-of-Life Care

medications plus continued breakthrough doses of short-acting opiates to be used as needed. Morphine and oxycodone are available in concentrated forms and sublingual formulations, which allow for rapid administration regardless of a patient's level of wakefulness or swallowing ability because of the small volumes needed per dose. Data do not appear to support the use of nebulized opiates for dyspnea at the end of life.<sup>15</sup>

### Delirium and Agitation

Patients often experience delirium and agitation in the last days and weeks of life.<sup>16</sup> Symptoms that do not cause the patient distress can be managed conservatively without medication. It is essential to assess for reversible or treatable causes of delirium, such as medication adverse effects, uncontrolled pain or discomfort, constipation, or urinary retention.

Antipsychotic medications such as haloperidol and risperidone (Risperdal) are effective in the treatment of delirium and agitation in end-of-life care.<sup>17</sup> Dosing for delirium tends to be significantly lower than for psychiatric disorders, such as schizophrenia.<sup>18,19</sup> Benzodiazepines should be used with caution for the treatment of agitation and delirium, because they can potentially provoke increased symptoms in older patients.<sup>20</sup> However, benzodiazepines can effectively treat anxiousness and agitation in the last hours and days of life because of their potentially sedating effects.

In patients with severe, refractory agitation, palliative sedation may be considered. Palliative sedation is defined as the intentional lowering of awareness toward, and including, unconsciousness for patients with severe and refractory symptoms. It should be considered only when symptoms do not respond to alternative therapies and should always be performed in consultation with a palliative medicine or hospice-trained clinician.<sup>21,22</sup> A "Curbside Consultation" article on this topic is available at <http://www.aafp.org/afp/2011/0501/p1094.html>.

### Nausea and Vomiting

Nausea and vomiting are common in end-of-life care. Multiple receptor pathways in the brain and in the gastrointestinal tract mediate nausea and vomiting. Medications that target dopaminergic pathways, such as haloperidol, risperidone, metoclopramide (Reglan), and prochlorperazine, are often used as first-line therapies for nausea because of their inhibition of receptors in the brain's chemoreceptor trigger zone.<sup>23,24</sup> Haloperidol and risperidone can be administered as oral liquid concentrates, and prochlorperazine can be administered via suppository if patients are unable to take pills.

Serotonin 5-HT<sub>3</sub> receptor antagonists, such as ondansetron (Zofran) and palonosetron (Aloxi), have been studied in chemotherapy- and radiation therapy-induced nausea, and are available as dissolvable tablets. In treating nausea at the end of life, studies have not shown these more costly 5-HT<sub>3</sub> medications to be superior to the older dopaminergic agents mentioned previously.<sup>25,26</sup>

When first-line agents are unable to control nausea, a second agent may be added. Anticholinergic medications such as meclizine (Antivert) or transdermal scopolamine can be added when a vestibular component of nausea is present. Corticosteroids, such as dexamethasone, have been studied for chemotherapy-induced nausea and are another potentially effective second-line agent for nausea control. Synthetic cannabinoid agents (e.g., dronabinol [Marinol]) and medical marijuana (in states where it is approved for medical use) can also be considered as second-line agents for nausea control. It should be noted that these second-line agents can provoke delirium and should be used with caution (*Table 2*).<sup>23-28</sup>

Severe constipation can lead to abdominal discomfort and nausea, which may improve with the treatment of constipation. Proactively managing a medication regimen that prevents constipation is a critical component of effective end-of-life care.

Vomiting can occur because of mechanical bowel obstruction. Malignant bowel obstruction is common with pelvic and gastrointestinal cancers.<sup>27</sup> Clinical symptoms of malignant bowel obstruction include nausea, vomiting, abdominal pain, and an inability to tolerate oral intake. When malignant bowel obstruction is suspected in end-of-life care, medical management with an antiemetic (e.g., haloperidol), as well as corticosteroids and analgesics, is recommended.<sup>28</sup> Octreotide (Sandostatin) has been used for the management of malignant bowel obstruction, but the data supporting its use are not robust.<sup>29</sup> Some patients with malignant bowel obstruction have a prophylactic venting gastrostomy tube placed earlier in the disease process to release pressure upstream of the obstruction and prevent vomiting. Caution should be used in placing new venting gastrostomy tubes in the final days of life because of the high risk of procedural complications and a lack of quality evidence showing prolongation of life.<sup>30</sup>

### Constipation

Effective management of constipation in end-of-life care is critical, because constipation can lead to pain, vomiting, restlessness, and delirium. Low oral intake of food and fluids and adverse effects of opiates are common etiologies. Preventive regimens generally include

**Table 2. Antiemetic Medications Used in End-of-Life Care**

Medication class	Medication (common as-needed dosage)	Comments
Anticholinergics	Scopolamine (1 or 2 1.5-mg patches applied topically and changed every 72 hours)	May also help to decrease oral secretions
Benzodiazepines	Lorazepam (Ativan; 0.5 to 2 mg orally or IV every 6 hours)	Consider in anticipatory nausea
Cannabinoids	Dronabinol (Marinol; 5 to 10 mg orally, rectally, or sublingually every 6 to 8 hours) Marijuana (recommended only in states where legal for medical use)	Consider in anticipatory nausea
Corticosteroids	Dexamethasone (2 to 8 mg orally or IV every 4 to 8 hours)	Consider in suspected malignant bowel obstruction or with increased intracranial pressure
Dopamine receptor antagonists	Haloperidol (0.5 to 2 mg orally or IV every 4 to 8 hours) Prochlorperazine (5 to 10 mg orally or IV every 6 to 8 hours) Chlorpromazine (12.5 to 25 mg IV or 25 to 50 mg orally every 6 to 8 hours) Metoclopramide (Reglan; 5 to 20 mg orally or IV every 6 hours)	Off-label use for nausea — — Consider in gastroparesis; avoid in suspected malignant bowel obstruction
Serotonin 5-HT <sub>3</sub> receptor antagonists	Ondansetron (Zofran; 4 to 8 mg orally or IV every 4 to 8 hours)	Available as oral disintegrating tablets

IV = intravenously.

Information from references 23 through 28.

a stimulant laxative (e.g., senna) with a stool softener (e.g., docusate [Colace], polyethylene glycol [Miralax]). Dosing regimens for these medications are listed in Table 3.<sup>31</sup> If constipation occurs despite preventive measures, prompt treatment with stronger laxatives, suppositories, or enemas is indicated. Methylnaltrexone (Relistor) is approved by the U.S. Food and Drug Administration for the treatment of opiate-related constipation that does not respond to traditional preventive and treatment regimens, although its higher cost often limits its use.<sup>32</sup>

### Oropharyngeal Secretions

It is common for patients to lose the ability to manage and clear their oropharyngeal secretions as they progress through the dying process.<sup>33</sup> This can result in a noisy breathing pattern, sometimes referred to as a death rattle. Generally, these secretions are not bothersome to the patient; rather, the family and caregivers are usually more troubled by the sound. A key component in reassuring family members and caregivers is good anticipatory guidance to normalize and destigmatize the breathing pattern. Although anticholinergic medications are often used to manage secretions, there is a lack of high-quality data to support their use.<sup>34</sup> Commonly used medications for treating excessive oropharyngeal secretions with

their usual starting dosages are shown in Table 4.<sup>33,34</sup> These medications include hyoscyamine (Levsin), atropine, glycopyrrolate (Robinul), and scopolamine.

### Fever

Treatment of fever at the end of life is based on the patient's life expectancy and goals of care. Fever may be treated with antipyretic medications such as

**Table 3. Medications for the Prevention and Treatment of Constipation in End-of-Life Care**

Medication	Dosage
Docusate (Colace)	1 or 2 tablets orally 2 times per day
Lactulose	15 to 30 mL orally 2 or 3 times per day
Magnesium hydroxide	30 to 60 mL orally at bedtime
Polyethylene glycol (Miralax)	1 tablespoon (17 g) dissolved in 4 to 8 oz of fluid orally per day
Senna with docusate	1 or 2 tablets orally 2 to 4 times per day

Adapted with permission from Clary PL, Lawson P. Pharmacologic pearls for end-of-life care. *Am Fam Physician.* 2009;79(12):1062.

**Table 4. Medications for the Treatment of Excessive Oropharyngeal Secretions in End-of-Life Care**

Medication	Dosage (as needed)
Atropine ophthalmic 1% drops	1 or 2 drops sublingually every 6 hours
Glycopyrrolate (Robinul)	1 mg orally or 0.2 to 0.4 mg subcutaneously or intravenously every 4 hours
Hyoscyamine (Levsin)	0.125 to 0.5 mg sublingually or subcutaneously every 4 hours
Scopolamine transdermal patch	1 or 2 1.5-mg patches applied every 72 hours

Information from references 33 and 34.

acetaminophen, nonsteroidal anti-inflammatory drugs, or corticosteroids, when appropriate. Acetaminophen suppositories can be safely administered in patients with impaired swallowing function. Conservative measures without medication may be considered if the fever is not causing secondary discomfort or if such measures are consistent with the patient’s and family’s goals of care.

**Final Comment**

Effective management of symptoms at the end of life is challenging but often can be achieved with fewer than four or five key medications (Table 5). Clinicians can help support patients and families through this process with the assurance that it will be as safe, dignified, and comfortable as medically possible.

This article updates a previous article on this topic by Clary and Lawson.<sup>31</sup>

**Data Sources:** A PubMed search was completed in Clinical Queries using the key terms hospice, palliative care, dyspnea, delirium, nausea, oropharyngeal secretion, death rattle, end-of-life care, fever, opiates, haloperidol, benzodiazepine, and malignant bowel obstruction. The search included meta-analyses, randomized controlled trials, clinical trials, and reviews. Also searched were the Agency for Healthcare Research and Quality evidence reports, Clinical Evidence, the Cochrane database, Database of Abstracts of Reviews of Effects, the Institute for Clinical Systems Improvement, the National Guideline Clearinghouse database, Essential Evidence Plus, and UpToDate. Search dates: January 26, 2016, and November 28, 2016.

**The Author**

ROSS H. ALBERT, MD, PhD, is chief of the Division of Palliative Medicine at Hartford Hospital and medical director at Hartford HealthCare at Home Hospice, Hartford, Conn.

Address correspondence to Ross H. Albert, MD, PhD, Hartford Hospital, 80 Seymour St., PO Box 5037, Hartford, CT 06102 (e-mail: ross.albert@hhhealth.org). Reprints are not available from the author.

**REFERENCES**

1. Institute of Medicine. *Dying in America: Improving Quality and Honoring Individual Preferences Near the End of Life*. Washington, DC: The National Academies Press; 2015.
2. Smith AK, Cenzer IS, Knight SJ, et al. The epidemiology of pain during the last 2 years of life. *Ann Intern Med*. 2010;153(9):563-569.
3. Abernethy AP, Currow DC, Frith P, Fazekas BS, McHugh A, Bui C. Randomised, double blind, placebo controlled crossover trial of sustained release morphine for the management of refractory dyspnoea. *BMJ*. 2003;327(7414):523-528.
4. Light RW, Muro JR, Sato RI, Stansbury DW, Fischer CE, Brown SE. Effects of oral morphine on breathlessness and exercise tolerance in patients with chronic obstructive pulmonary disease. *Am Rev Respir Dis*. 1989; 139(1):126-133.
5. Bruera E, MacEachern T, Ripamonti C, Hanson J. Subcutaneous morphine for dyspnea in cancer patients. *Ann Intern Med*. 1993;119(9):906-907.

**Table 5. Common End-of-Life Medications: the Hospice Comfort Kit**

Medication class	Medication	Initial suggested dosage
Antipsychotics	Haloperidol or risperidone (Risperdal; both 2 mg per mL)	0.5 to 1 mg sublingually or rectally every 4 hours as needed for agitation or nausea
Antipyretics	Acetaminophen suppository (650 mg)	650 mg orally or rectally every 4 hours as needed for fever
Benzodiazepines	Lorazepam (Ativan; 2 mg per mL)	0.5 to 1 mg sublingually or rectally every 4 hours as needed for anxiety
Opiates	Morphine or oxycodone (both 20 mg per mL)	5 to 10 mg sublingually every 3 hours as needed for pain or shortness of breath
Secretion medications	Hyoscyamine (Levsin; 0.125-mg sublingual tablet/liquid) or atropine ophthalmic 1% drops	0.125 mg of hyoscyamine or 2 or 3 drops of atropine sublingually every 6 hours as needed for oropharyngeal secretions

6. Mularski RA, Reinke LF, Carrieri-Kohlman V, et al.; ATS Ad Hoc Committee on Palliative Management of Dyspnea Crisis. An official American Thoracic Society workshop report: assessment and palliative management of dyspnea crisis. *Ann Am Thorac Soc*. 2013;10(5):S98-S106.
7. Groninger H, Vijayan J. Pharmacologic management of pain at the end of life. *Am Fam Physician*. 2014;90(1):26-32.
8. Claessens MT, Lynn J, Zhong Z, et al. Dying with lung cancer or chronic obstructive pulmonary disease: insights from SUPPORT. Study to Understand Prognoses and Preferences for Outcomes and Risks of Treatments. *J Am Geriatr Soc*. 2000;48(5 suppl):S146-S153.
9. McCarthy M, Lay M, Addington-Hall J. Dying from heart disease. *J R Coll Physicians Lond*. 1996;30(4):325-328.
10. Addington-Hall J, Lay M, Altmann D, McCarthy M. Symptom control, communication with health professionals, and hospital care of stroke patients in the last year of life as reported by surviving family, friends, and officials. *Stroke*. 1995;26(12):2242-2248.
11. Voltz R, Borasio GD. Palliative therapy in the terminal stage of neurological disease. *J Neurol*. 1997;244(suppl 4):S2-S10.
12. Campbell ML, Templin T, Walch J. A Respiratory Distress Observation Scale for patients unable to self-report dyspnea. *J Palliat Med*. 2010;13(3):285-290.
13. Mahler DA, O'Donnell DE. Recent advances in dyspnea. *Chest*. 2015;147(1):232-241.
14. Portenoy RK, Sibirceva U, Smout R, et al. Opioid use and survival at the end of life: a survey of a hospice population. *J Pain Symptom Manage*. 2006;32(6):532-540.
15. Jennings AL, Davies AN, Higgins JP, Broadley K. Opioids for the palliation of breathlessness in terminal illness. *Cochrane Database Syst Rev*. 2001;(4):CD002066.
16. Goy ER, Ganzini L. Prevalence and natural history of neuropsychiatric syndromes in veteran hospice patients. *J Pain Symptom Manage*. 2011;41(2):394-401.
17. Grassi L, Caraceni A, Mitchell AJ, et al. Management of delirium in palliative care: a review. *Curr Psychiatry Rep*. 2015;17(3):550.
18. Seitz DP, Gill SS, van Zyl LT. Antipsychotics in the treatment of delirium: a systematic review. *J Clin Psychiatry*. 2007;68(1):11-21.
19. Boettger S, Breitbart W. Atypical antipsychotics in the management of delirium: a review of the empirical literature. *Palliat Support Care*. 2005;3(3):227-237.
20. Marcantonio ER, Juarez G, Goldman L, et al. The relationship of postoperative delirium with psychoactive medications. *JAMA*. 1994;272(19):1518-1522.
21. American Academy of Hospice and Palliative Medicine. Statement on palliative sedation. 2014. <http://aahpm.org/positions/palliative-sedation>. Accessed November 28, 2016.
22. Kirk TW, Mahon MM; Palliative Sedation Task Force of the National Hospice and Palliative Care Organization Ethics Committee. National Hospice and Palliative Care Organization (NHPCO) position statement and commentary on the use of palliative sedation in imminently dying terminally ill patients. *J Pain Symptom Manage*. 2010;39(5):914-923.
23. Markowitz AJ, Rabow MW. Management of intractable nausea and vomiting in patients at the end of life: "I was feeling nauseous all of the time...nothing was working." *JAMA*. 2008;299(15):1826.
24. Büttner M, Walder B, von Elm E, Tramèr MR. Is low-dose haloperidol a useful antiemetic? A meta-analysis of published and unpublished randomized trials. *Anesthesiology*. 2004;101(6):1454-1463.
25. Weschules DJ, Maxwell T, Reifsnnyder J, Knowlton CH. Are newer, more expensive pharmacotherapy options associated with superior symptom control compared to less costly agents used in a collaborative practice setting? [published correction appears in *Am J Hosp Palliat Care*. 2006;23(5):427]. *Am J Hosp Palliat Care*. 2006;23(2):135-149.
26. Hardy J, Daly S, McQuade B, et al. A double-blind, randomised, parallel group, multinational, multicentre study comparing a single dose of ondansetron 24 mg p.o. with placebo and metoclopramide 10 mg t.d.s. p.o. in the treatment of opioid-induced nausea and emesis in cancer patients. *Support Care Cancer*. 2002;10(3):231-236.
27. Tuca A, Guell E, Martinez-Losada E, Codorniu N. Malignant bowel obstruction in advanced cancer patients: epidemiology, management, and factors influencing spontaneous resolution. *Cancer Manag Res*. 2012;4:159-169.
28. Feuer DJ, Broadley KE. Corticosteroids for the resolution of malignant bowel obstruction in advanced gynaecological and gastrointestinal cancer. *Cochrane Database Syst Rev*. 2000;(2):CD001219.
29. Currow DC, Quinn S, Agar M, et al. Double-blind, placebo-controlled, randomized trial of octreotide in malignant bowel obstruction. *J Pain Symptom Manage*. 2015;49(5):814-821.
30. Cousins SE, Tempest E, Feuer DJ. Surgery for the resolution of symptoms in malignant bowel obstruction in advanced gynaecological and gastrointestinal cancer. *Cochrane Database Syst Rev*. 2016;(1):CD002764.
31. Clary PL, Lawson P. Pharmacologic pearls for end-of-life care. *Am Fam Physician*. 2009;79(12):1059-1065.
32. Chamberlain BH, Cross K, Winston JL, et al. Methylnaltrexone treatment of opioid-induced constipation in patients with advanced illness. *J Pain Symptom Manage*. 2009;38(5):683-690.
33. Lokker ME, van Zuylen L, van der Rijt CC, van der Heide A. Prevalence, impact, and treatment of death rattle: a systematic review. *J Pain Symptom Manage*. 2014;47(1):105-122.
34. Wee B, Hillier R. Interventions for noisy breathing in patients near to death. *Cochrane Database Syst Rev*. 2008;(1):CD005177.