*Graeme M Rocker, MHS, DM, FRCP,
FRCPC¹*

Deborah Cook, MD, MSc(Epid), FRCPC²

¹ Professor of Medicine
Dalhousie University, QEII Health Sciences
Centre

Head, Division of Respiriology
#4457 Halifax Infirmary
1796 Summer Street, Halifax, NS, B3H 3A7

² Professor of Medicine, Clinical Epidemiology
& Biostatistics

Academic Chair, Critical Care Medicine
D176 St Joseph's Healthcare Hamilton
50 Charlton Avenue East, Hamilton, ON L8N
4A6

'INSPIRED' Approaches to Better Care for Patients with Advanced COPD

Abstract

Chronic Obstructive Pulmonary Disease (COPD) is the most common cause of admission to acute care facilities in Canada. The burden of illness for patients, caregivers and the health care system is profound. Dyspnea in advanced COPD pervades all aspects of patients' lives. When increasing symptom burden limits patients to their homes, crucial primary care services become less accessible, and care of end-stage COPD becomes increasingly fragmented and reactive. Given the considerable physical and psychosocial consequences of advanced COPD, this phase can be devastating for patients and families. In this article we outline the need for clinical interventions and re-organized models of care designed for better continuity to achieve more favorable outcomes for these patients and their families. Outreach programs and use of personalized action plans that include advice on careful use of opioids can be remarkably effective. The move toward an integrated approach to COPD management with more effective advance care planning will help patients and their families make informed decisions throughout the illness trajectory. Intensive medical treatment focused on increasing survival can coexist with both holistic and palliative approaches to improve the quality of life of patients with severe end-stage COPD.

Clin Invest Med 2013; 36 (3): E114-E120.

Correspondence to:

Dr. Graeme Rocker
Dalhousie University, QEII Health Sciences Centre
#4457 Halifax Infirmary
1796 Summer Street, Halifax, NS, B3H 3A7
e-mail: gmrocker@dal.ca

Compelling data from the UK in 2000 demonstrated that patients who live with advanced chronic obstructive pulmonary disease (COPD) suffer with a lower quality of life than do patients with non small cell lung cancer [1]. In Canada, COPD is the fourth leading cause of death (<http://www.statcan.gc.ca/pub/84-215-x/2012001/table-tableau/tbl001-eng.htm>) and, as a diagnosis, is responsible for the highest proportion of acute admissions to hospitals in Canada [2]. Index admission mortality generally ranges between two and 10% [3,4]. The typical pattern for survivors is a relentless decline in lung function and impaired quality of life. COPD serves as an excellent example of a chronic illness where the traditional biomedical approach of intensive episodic care fails patients and families.

Dyspnea, as the predominant symptom is responsible for more admissions to acute care facilities than any other symptom. Dyspnea is nearly universal and, in advanced COPD, often refractory to conventional treatments [5]. For many patients, dyspnea pervades all aspects of their lives and is a source of serious disability. As dyspnea progresses, patients may be rendered housebound and experience profound social isolation [6]. When increasing symptom burden limits patients' ability to get out of their homes for non-emergent assessment, crucial primary care services become less accessible and care of end-stage COPD becomes increasingly 'fragmented, episodic and reactive' [7]. Thus, patients are often caught in a cycle wherein they present to the emergency room, are admitted to hospital, then, after acute management, they are discharged without having their long term care needs met [8].

Patients and their families living with end-stage COPD can tell us what we need to know to change our health care system for the better. In multicentre studies, patients reported that it is very important to them that we provide them with available supports after they return home following hospitalization [9]. Patients at high risk of frequent acute exacerbations of COPD (AECOPD) should be provided with a written 'action plan' as per professional society guidelines [10] to ensure that they can activate treatments at home when they experience signs and symptoms consistent with an AECOPD. Professional societies have espoused the use of 'action plans', but emphasize the need for *effective* education and reinforcement [11]. Recent randomized trials in Canada [12], the US [13] and Europe [14] have confirmed the efficacy of action plans within a broader model of self-management. Reductions in emergency room visits and hospital readmission rates were similar in the three studies: at about 40%. A meta-analysis of implementing self-management education for patients enrolled in 14 studies (both randomized and non-randomized) confirmed improvements in health status and reduction in subsequent hospital

admissions [15]; however, one recent, randomized trial of patient self-management for patients with COPD was terminated early due to increased mortality in the intervention cohort [16]. The reasons for increased mortality are not clear, and this approach needs further intensive study. Given the monumental costs associated with provision of acute care services to patients with AECOPD [17], strategies to avoid repeated hospital admissions should be a priority to health care administrators.

This says nothing of lightening the burdens of patients who live with COPD and who describe how an exacerbation and its associated dyspnea is akin to a 'near death experience' [18]. Some patients feel abandoned by the healthcare team in the advanced stages of the disease. Abandonment of patients is reflected in the use of the inappropriate phrase: 'there is nothing more we can do for you.' For patients and families, this phrase can be devastating, given the considerable physical and psychosocial consequences of advanced COPD [19]. Re-organized models of care and clinical interventions with a goal of achieving more favorable outcomes for these patients and their families are needed to overcome the pervasive sense of nihilism that exists for some patients in some settings.

Current Approaches to Managing Dyspnea in Advanced COPD

The Canadian Thoracic Society (CTS) has recently released a clinical practice guideline [20] (available via www.copdguidelines.ca) that presents an evidence-based approach to dyspnea management (see Figure 1).

This clinical practice guideline [20] builds on the concept of the 'dyspnea ladder' described some years ago [21] and emphasizes a stepwise approach to palliation of refractory dyspnea using conventional therapies, non-pharmacological approaches and carefully initiated and titrated opioids.

Gaps in Care

Much has been written about the merits of alternative models of care to address the needs of patients and caregivers who are living with advanced COPD [22-25]. Patients and family caregivers have repeatedly given voice to these concepts [7,9,26]. We should be building comprehensive, integrated programs of care to respond to their needs. Disease-specific self-management strategies can reduce emergency room utilization and hospital admissions [12,13]. Adding these programs to conventional care without a well thought out, comprehensive, integrated approach is likely to fall short of optimal effectiveness and efficiency. Important elements to consider include

FIGURE 1. Comprehensive approach to management of dyspnea in patients with advanced COPD

ICS, Inhaled corticosteroids; LAAC, Long-acting anticholinergics; LABA, Long-acting beta-2 agonists; NMES, Neuromuscular electrical stimulation; O₂, Oxygen; PDE₄, Phosphodiesterase 4; SABD, Short-acting bronchodilators. Obtained/modified from Marciniuk et al. [20].

robust physician support, a detailed plan based on patient-driven goals of care and inclusive of an individualized 'action plan' to deal with crisis symptoms in the home [27] when fear and anxiety overwhelms the patient and caregiver (Figure 2).

Outreach for Patients with Advanced COPD

Chronic care for COPD must reach beyond the primary care practice into patients' lives in the community on one hand, and yet link into emergency room and inpatient practices on the other hand [23]. One example of an innovative, evidence-based program that embodies this philosophy is the INSPIRED program in Halifax, Nova Scotia, Canada: an acronym for *Implementing a Novel and Supportive Program of Individualized Care for Patients and Families Living with Respiratory Disease*. Eligible patients are identified during hospital admission and, after discharge, they enrol in a structured program that provides dedicated case management, orchestrated by a skilled respiratory therapist educator who also acts as a care coordinator across care transitions. The care coordinator is supported by other respiratory therapists, a respirologist with interest and expertise in community-based care for patients with advanced COPD and a spiritual care practitioner to address advance care

planning issues. Patients are followed in their homes with bi-weekly visits spanning over a period of approximately four months. Emphasis is placed on providing proactive care through home-based self-management, provision of individualized action plans for both acute exacerbations of COPD and dyspnea crises, sensitive advance care planning in the home, plus help with navigating the local healthcare system to gain access to allied support services. Preliminary analysis of an initial cohort [28] who completed the full program revealed that participation in INSPIRED was associated with a 70% reduction in subsequent emergency room visits, hospital admissions and hospital length of stay. This improvement in care has been sustained for more than 80 patients for over six months beyond their program completion.

Avoiding visits to the emergency room may be impossible for some patients and families who are overwhelmed by panic, and who for years have been conditioned to be reliant upon acute hospital care when they are in crisis. In a recent study of the feasibility of implementing a program of palliative care for patients with advanced COPD [29], we found that despite access to comprehensive medical support, which included individualized action plans and after-hours physician response,

Action Plan for Shortness of Breath (dyspnea)

Created for: [Patient Name +/- ID number]

Date: [Insert date plan was created]

A good morning routine to minimize shortness of breath first thing in the morning:

- Take 5 breaths from your incentive spirometer (slowly open airways). Use 4 times daily as needed
- Huffing/cough to clear your airway. Do your pursed-lip breathing if this helps
- Use your blue puffer, gray handihaler, and purple puffer as directed (don't forget to use your aerochamber and rinse after your purple puffer). Your blue puffer may be used as often as every four hours as needed
- Take your long-acting opioid medication [insert name, dose] as directed

When more short of breath than usual:

- With a slight increase in your shortness of breath at rest (not a result of infection or "crisis"), you can use an extra [insert dose] of your opioid syrup every 1-2 hours as needed for 'breakthrough' dyspnea between your regular doses
- For predictable shortness of breath with activity (i.e. getting up, dressed, bathed), time these activities ½ hour after your puffers and opioid dosing

For "crisis" shortness of breath (not due to infection) comes on suddenly, catches you by surprise:

- Use your hand-held fan and do pursed-lip breathing. Try recovery positions
- Use 2 puffs of your blue puffer (with aerochamber) or try your nebule instead
- Adjust oxygen flow from ____ to ____ litres/min for 10-15 mins only then re-adjust back to ____
- Take your anti-anxiety medication [insert name, dose], 1 tablet under the tongue
- If not settling, use Fentanyl, 12.5 ug from pre-prepared syringe. Let liquid dissolve under the tongue. Repeat in 10 mins if still not settling and call 911

For flare ups of COPD with increased sputum volume and mucky colour, use antibiotics and prednisone as per your COPD action plan.

FIGURE 2. Sample of a personalized action plan for dyspnea

some patients continued to turn repeatedly to the emergency room when symptoms escalated rapidly [29].

Communication and Advance Care Planning

A lack of timely communication and comprehensive care planning is common in the fragmented approach to care for those with advanced COPD. To help address this lack of planning, the INSPIRED program has incorporated an in-home advance care planning component.

The *Respecting Choices* model defines advance care planning as an organized ongoing process of communication to help an individual understand, reflect upon and discuss goals, values and beliefs for future his/her future care [30], including healthcare decisions (see Figure 2). More often than not, advanced care planning is reduced to a clinician-centred, one time 'code status' discussion that tends to occur during an illness crisis [31] and in a suboptimal setting such as the ER or ICU [30]. When patients have not previously considered or discussed their values and care preferences in terms of quality of life, dignity, respect, death, care and who they might choose as a substitute decision-maker, being asked to do so in an already emotionally charged crisis atmosphere can add unnecessary suffering.

The value of timely, effective advanced care planning cannot be understated. Such discussion can help patients and loved ones begin to prepare themselves emotionally for illness progression. In terms of potential impact, sensitive, timely discussion and decisions may increase the likelihood that a patient's end of life care wishes will be known and followed. This can decrease the stress for family members and potential for complicated grief following a patient's death, minimize ethical distress for staff and increase satisfaction with care for family members [32]. When patients with COPD more fully understand the range and implications of life-sustaining treatments available, they tend to choose fewer life-sustaining procedures or, at most, a time-limited trial of specific life-sustaining interventions. This lowers the rates of unwanted admissions to the intensive care unit and associated costs in the final weeks of a patient's life [33].

In summary, advance care planning as a patient-centred, on-going process of identifying and adjusting goals of care -- it is much more than a means to an end(34). It is about improving care throughout the illness trajectory, not just at the end of life.

Opioids

An increasing body of evidence supports the use and safety of opioids for refractory dyspnea in patients with advanced COPD. Nevertheless, long-held fears of further depressing respiration continue to limit more widespread acceptance by physicians [35] despite recommendations for their use in several recent professional society statements and/or clinical practice guidelines [20,36,37]. Qualitative studies indicate efficacy and acceptability from patient and caregiver perspectives [35]. In contrast, physicians from general practice, internal medicine, palliative care and respirology suggested that lack of education and knowledge concerning opioids were among the greatest barriers to opioid use in advanced COPD [35]. They also worried about possible censure for prescribing opioids in this context. Distinctions were made between prescribing opioids for cancer (for which clear guidelines are available), and prescribing for dyspnea in advanced COPD (for which many considered opioids to be outside the standard of care) [35].

Data from recently completed or ongoing clinical trials are encouraging, with benefit outweighing side effects and patients finding them beneficial over months of usage [38,39]. Our own clinical trial experience suggests that an initial 'start low, go slow' approach works well [20,38]. Often patients are reticent to try opioids, associating them with impending death. Sensitive explanations usually diffuse concerns [35,38] and patients find it convenient to move to a sustained-release preparation taken daily or twice daily (after daily requirements of an immediate-release preparation are established), with additional immediate-release opioid for 'breakthrough' dyspnea.

Clinicians should be aware that current opioid product monographs continue to counsel explicitly against their use for patients with respiratory disease, despite the absence of any supporting evidence that they might be detrimental.

The Final Days

While death at home might seem the ideal outcome, for patients with respiratory disease this may not be a realistic goal. Caregivers are often burnt out after years of living with a patient with a high symptom burden over a long trajectory. The caregivers may not have the capacity to cope with the additional demands of a home-based respiratory death at home. A hospital death in these circumstances should not be considered a failure. Success might be viewed through a different lens; whereby the dying begins at home but the death occurs in the hospital. Success might be considered in the light of averted visits to the emergency room, or through a short final hospital

admission without the intrusion of CPR as we have recently described [29].

Conclusions

Our healthcare system is faced with the need to care for an aging population significantly burdened with chronic illnesses and frailty [40,41]. As the prevalence of COPD rises, more patients and families will live with the burdens of advanced or end-stage COPD than ever before. The move toward an integrated care approach to COPD will help patients and their families reach informed decisions about their care throughout the trajectory of COPD. Intensive medical treatment focused on increasing survival, as well as holistic and palliative approaches focused on optimizing quality of life are no longer mutually exclusive across the spectrum of care.

Acknowledgement

Dr Rocker thanks Capital District Health Authority for confirmation of 'INSPIRED' as a core program and GlaxoSmith-Kline for their support that enabled us to pilot and then sustain INSPIRED beyond its early iterations. D Cook is supported by a Canada Research Chair.

References

1. Gore JM, Brophy CJ, Greenstone MA. How well do we care for patients with end stage chronic obstructive pulmonary disease (COPD)? A comparison of palliative care and quality of life in COPD and lung cancer. *Thorax*. 2000 Dec;55(12):1000-6. PubMed PMID: 15.
2. Health Indicators 2008. Canadian Institute of Health Information. Page 21. .
3. Steer J, Gibson J, Bourke SC. The DECAF Score: predicting hospital mortality in exacerbations of chronic obstructive pulmonary disease. *Thorax*. 2012 Nov;67(11):970-6. PubMed PMID: 22895999.
4. Tabak YP, Sun X, Johannes RS, Gupta V, Shorr AF. Mortality and need for mechanical ventilation in acute exacerbations of chronic obstructive pulmonary disease: development and validation of a simple risk score. *Arch Intern Med*. 2009 Sep 28;169(17):1595-602. PubMed PMID: 19786679.
5. Horton R, Rocker G. Contemporary issues in refractory dyspnoea in advanced chronic obstructive pulmonary disease. *Curr Opin Support Palliat Care*. 2010 Jun;4(2):56-62. PubMed PMID: 20407378. Epub 2010/04/22. eng.
6. Elkington H, White P, Addington-Hall J, Higgs R, Edmonds P. The healthcare needs of chronic obstructive pulmonary disease patients in the last year of life. *Palliat Med*. 2005 Sep;19(6):485-91. PubMed PMID: 16218161.
7. Crawford GB, Brooksbank MA, Brown M, Burgess TA, Young M. The unmet needs of people with end-stage chronic obstructive pulmonary disease: recommendations for change in Australia. *Intern Med J*. 2012 Apr 4. PubMed PMID: 22471972. Epub 2012/04/05. Eng.
8. Bailey PH. The dyspnea-anxiety-dyspnea cycle--COPD patients' stories of breathlessness: "It's scary /when you can't breathe". *Qual Health Res*. 2004 Jul;14(6):760-78. PubMed PMID: 15200799.
9. Rocker GM, Dodek PM, Heyland DK. Toward optimal end-of-life care for patients with advanced chronic obstructive pulmonary disease: Insights from a multicentre study. *Can Respir J*. 2008 July/August;15(5):249-54. PubMed PMID: 18716686.
10. O'Donnell DE, Aaron S, Bourbeau J, Hernandez P, Marciniuk DD, Balter M, et al. Canadian Thoracic Society recommendations for management of chronic obstructive pulmonary disease - 2007 update. *Can Respir J*. 2007 Sep;14 Suppl B:5B-32B. PubMed PMID: 17885691. Epub 2007/11/24. eng.
11. Nici L, ZuWallack R. An official American Thoracic Society workshop report: the Integrated Care of The COPD Patient. *Proc Am Thorac Soc*. 2012 Mar;9(1):9-18. PubMed PMID: 22421582. Epub 2012/03/17. eng.
12. Bourbeau J, Julien M, Maltais F, Rouleau M, Beaulieu A, Begin R, et al. Reduction of hospital utilization in patients with chronic obstructive pulmonary disease: a disease-specific self-management intervention. *Arch Intern Med*. 2003 Mar 10;163(5):585-91. PubMed PMID: 12622605. Epub 2003/03/08. eng.
13. Rice KL, Dewan N, Bloomfield HE, Grill J, Schult TM, Nelson DB, et al. Disease management program for chronic obstructive pulmonary disease: a randomized controlled trial. *Am J Respir Crit Care Med*. 2010 Oct 1;182(7):890-6. PubMed PMID: 20075385. Epub 2010/01/16. eng.
14. Casas A, Troosters T, Garcia-Aymerich J, Roca J, Hernandez C, Alonso A, et al. Integrated care prevents hospitalisations for exacerbations in COPD patients. *Eur Respir J*. 2006 Jul;28(1):123-30. PubMed PMID: 16611656. Epub 2006/04/14. eng.
15. Effing T, Monnikhof EM, van der Valk PD, van der Palen J, van Herwaarden CL, Partidge MR, et al. Self-management education for patients with chronic obstructive pulmonary disease. *Cochrane Database Syst Rev*. 2007 (4):CD002990. PubMed PMID: 17943778. Epub 2007/10/19. eng.
16. Fan VS, Gaziano JM, Lew R, Bourbeau J, Adams SG, Leatherman S, et al. A Comprehensive Care Management Program to Prevent Chronic Obstructive Pulmonary Disease Hospitalizations: A Randomized, Controlled Trial. *Ann Intern Med*. 2012 May 15;156(10):673-83. PubMed PMID: 22586006. Epub 2012/05/16. Eng.
17. Mittmann N, Kuramoto L, Seung SJ, Haddon JM, Bradley-Kennedy C, Fitzgerald JM. The cost of moderate and

- severe COPD exacerbations to the Canadian healthcare system. *Respir Med*. 2008 Mar;102(3):413-21. PubMed PMID: 18086519. Epub 2007/12/19. eng.
18. Bailey PH. Death stories: acute exacerbations of chronic obstructive pulmonary disease. *Qual Health Res*. 2001 May;11(3):322-38. PubMed PMID: 11339077.
19. Rocker GM, Young J, Simpson AC. Advanced chronic obstructive lung disease: more than a lung disease. *Prog Palliat Care*. 2009;17:117-25.
20. Marciniuk DD, Goodridge D, Hernandez P, Rocker G, Balter M, Bailey P. et al for the Canadian Thoracic Society COPD Committee Dyspnea Expert Working Group. Managing dyspnea in patients with advanced chronic obstructive pulmonary disease: A Canadian Thoracic Society clinical practice guideline. *Can Respir J*. 2011;18(2):1-10.
21. Rocker GM, Sinuff T, Horton R, Hernandez P. Advanced Chronic Obstructive Pulmonary Disease: Innovative Approaches to Palliation. *J Palliat Med*. 2007;10(3):783-97.
22. Simpson AC, Rocker GM. Advanced chronic obstructive pulmonary disease: rethinking models of care. *Qjm*. 2008 Sep;101(9):697-704. PubMed PMID: 18669555.
23. Fromer L. Implementing chronic care for COPD: planned visits, care coordination, and patient empowerment for improved outcomes. *Int J Chron Obstruct Pulmon Dis*. 2011;6:605-14. PubMed PMID: 22162647. Epub 2011/12/14. eng.
24. Ortiz G, Fromer L. Patient-Centered Medical Home in chronic obstructive pulmonary disease. *J Multidiscip Healthc*. 2011;4:357-65. PubMed PMID: 22096340. Epub 2011/11/19. eng.
25. Booth S, Bausewein C, Rocker G. New models of care for advanced lung disease. *Prog Palliat Care*. 2011;19:254-63.
26. White P, White S, Edmonds P, Gysels M, Moxham J, Seed P, et al. Palliative care or end-of-life care in advanced chronic obstructive pulmonary disease: a prospective community survey. *Br J Gen Pract*. 2011 Jun;61(587):e362-70. PubMed PMID: 21801516. Epub 2011/08/02. eng.
27. Horton R. Reducing emergency room utilization in end-stage COPD - feasible or fantasy? *Chron Respir Dis*. 10(1):49-54. PubMed PMID: 23355405. Epub 2013/01/29. eng.
28. Young J, Simpson AC, Demmons J, Conrad W, Rocker G. Evaluating The Impacts Of "INSPIRED": A New Outreach Program For Patients And Families Living With Advanced Chronic Obstructive Pulmonary Disease (COPD). *Am J Respir Crit Care Med*. 2012;185:A3732.
29. Horton R, Rocker G, Dale A, Young J, Hernandez P, Sinuff T. Implementing a Palliative Care Trial in Advanced COPD: A Feasibility Assessment (The COPD IMPACT Study). *J Palliat Med*. 2013 Jan;16(1):67-73. PubMed PMID: 23317322. Epub 2013/01/16. eng.
30. Patel K, Janssen DJ, Curtis JR. Advance care planning in COPD. *Respirology*. 2012 Jan;17(1):72-8. PubMed PMID: 22008225. Epub 2011/10/20. eng.
31. Barnard D. Advance care planning is not about "getting it right". *J Palliat Med*. 2002 Aug;5(4):475-81. PubMed PMID: 12243673. Epub 2002/09/24. eng.
32. Wright AA, Zhang B, Ray A, Mack JW, Trice E, Balboni T, et al. Associations between end-of-life discussions, patient mental health, medical care near death, and caregiver bereavement adjustment. *JAMA*. 2008 Oct 8;300(14):1665-73. PubMed PMID: 18840840. Epub 2008/10/09. eng.
33. Au DH, Udris EM, Fihn SD, McDonnell MB, Curtis JR. Differences in health care utilization at the end of life among patients with chronic obstructive pulmonary disease and patients with lung cancer. *Arch Intern Med*. 2006 Feb 13;166(3):326-31. PubMed PMID: 16476873.
34. Sudore RL, Fried TR. Redefining the "planning" in advance care planning: preparing for end-of-life decision making. *Ann Intern Med*. 2010 Aug 17;153(4):256-61. PubMed PMID: 20713793. Epub 2010/08/18. eng.
35. Rocker G, Young J, Donahue M, Farquhar M, Simpson C. Perspectives of patients, family caregivers and physicians about the use of opioids for refractory dyspnea in advanced chronic obstructive pulmonary disease. *CMAJ*. 2012 Jun 12;184(9):E497-504. PubMed PMID: 22529167. Epub 2012/04/25. eng.
36. Lanken PN, Terry PB, Delisser HM, Fahy BF, Hansen-Flaschen J, Heffner JE, et al. An official American Thoracic Society clinical policy statement: palliative care for patients with respiratory diseases and critical illnesses. *Am J Respir Crit Care Med*. 2008 Apr 15;177(8):912-27. PubMed PMID: 18390964.
37. Mahler DA, Selecky PA, Harrod CG, Benditt JO, Carrieri-Kohlman V, Curtis JR, et al. American College of Chest Physicians consensus statement on the management of dyspnea in patients with advanced lung or heart disease. *Chest*. 2010 Mar;137(3):674-91. PubMed PMID: 20202949. Epub 2010/03/06. eng.
38. Rocker GM, Simpson AC, Joanne Young B, Horton R, Sinuff T, Demmons J, et al. Opioid therapy for refractory dyspnea in patients with advanced chronic obstructive pulmonary disease: patients' experiences and outcomes. *Canadian Medical Association Open Access Journal*. 2013 January 16, 2013;1(1):E27-E36.
39. Currow DC, McDonald C, Oaten S, Kenny B, Allcroft P, Frith P, et al. Once-daily opioids for chronic dyspnea: a dose increment and pharmacovigilance study. *J Pain Symptom Manage*. 2011 Sep;42(3):388-99. PubMed PMID: 21458217. Epub 2011/04/05. eng.
40. Lynn J. Palliative Care Beyond Cancer: Reliable comfort and meaningfulness. *BMJ*. 2008 Apr 26;336(7650):958-9. PubMed PMID: 18397941. Epub 2008/04/10. eng.
41. Murray SA, Sheikh A. Palliative Care Beyond Cancer: Care for all at the end of life. *Bmj*. 2008 Apr 26;336(7650):958-9. PubMed PMID: 18397942.