

Interventions to Manage Symptoms at the End of Life

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ABSTRACT

The aim of this article is to summarize the current evidence base about interventions that improve symptoms at the end of life. Moderate to severe symptoms are highly prevalent in the weeks and months before death: 1.4 million individuals have dyspnea; and 1 million have pain. Of those with pain, 300,000 want more pain relief. 700,000 may need more relief, but do not receive it because of the myth of opioid addiction; their physicians do not know how to manage the adverse effects of pain relieving therapies, or they don't know the various options that are available for pain relief. Of the 1 million Americans who die in hospitals, 324,000 had fatigue, 280,000 anorexia, 244,000 dyspnea, 232,000 xerostomia, 208,000 cough, 196,000 pain, 148,000 confusion, 148,000 depression, 140,000 nausea, 92,000 insomnia in 23, and 88,000 vomiting. This is caused in part by clinician ignorance. In a representative sample of oncologists, the most important source of information about symptom control was trial-and-error in practice. In addition, large, well-designed, well-controlled studies of patients at the end of life have not been performed. Clinical practice is guided by extrapolation of data from other populations and from anecdote. The system of care provided by hospice programs in the U.S. provides improved symptom control as compared with hospitals, home health agency, and nursing home systems.

Population-based studies of prevalence are needed to gauge outcomes of the implementation of measures to relieve symptoms. Well-powered, definitive studies of both existing and new approaches in terminally ill patients with the most common symptoms are needed. The health care system interventions that are effective in hospice care must be studied so that they can be broadly applied to the care of all dying Americans.

INTRODUCTION

THE PURPOSE OF THIS PAPER is to summarize the current knowledge base about interventions that improve symptoms at the end-of-life with the goal of making some recommendations about the direction that future scientific research should take. The first challenge in such a task is to define the end-of-life. Although there is no particular scientific rationale for it, a regulatory convention in the U.S. is to consider the last 6 months of

life. If we were to consider the behavior of physicians and others, the end-of-life would be the last days to weeks because that is when some (but not all) health care professionals can identify that the end-of-life is near and change their treatment patterns. If we were to consider the epidemiologists, they would have us consider the months to years of life for patients with a disease or symptom complex who will foreseeably die from the condition. Finally, the theologians might argue that because we all die eventually, all of life is end-of-

life care. This variability in defining end-of-life care is more than semantic. It has a direct bearing on evaluating the scientific basis for managing symptoms. For the purposes of this paper, I will be looking at the evidence for controlling symptoms in the last weeks and months. That should not be taken to imply that symptom control is not important anywhere in the course of illness, whether terminal or not; it is important. In fact, the emerging field of palliative care specifically stakes out the relief of suffering and improvement of quality of life from the presentation of illness to death.¹ This manuscript only looks at symptom management at that far right hand portion of the disease trajectory.

I will structure this paper in four parts. First I will summarize what we know about the prevalence of symptoms at the end of life. This is important to establish an estimate of the magnitude of the symptom burden of patients who are at the end of life. Second, I will look at the evidence that physicians, nurses, and other health professionals know the existing knowledge base. This is important because any deficits in symptom control from prevalence data can partly be explained by the fact that health care professionals do not have appropriate education in symptom control. Third, I will summarize the evidence base for the management of symptoms at the end of life. Finally, I will review what we know about systems that ensure that the existing evidence is reliably and routinely applied to the patients who need it. We know that even if we have the scientific evidence, and the health care professionals have the attitudes, knowledge, and skills to apply it, if the systems do not support the appropriate behavior the patients will not receive the benefits of the evidence.²

PREVALENCE

The symptom burden for patients at the end of life is high. Although population-based data are not captured as a routine feature of health statistics in the U.S., one study performed within the last 10 years surveyed a representative sample of 988 Americans living at home identified by their physicians as being terminally ill with a prognosis of less than 6 months.³ In this sample, 71% had shortness of breath, 50% had moderate to severe pain, 36% were incontinent of urine or feces, and 18% were fatigued enough to spend more than

50% of their waking hours in bed.⁴ Symptom prevalence was the same no matter what the underlying disease.

If we use this study to estimate prevalence of symptoms of terminally ill patients at home, we come up with startling numbers. There are about 2.4 million deaths in the U.S. each year. About 10% of those are sudden in nature; the remaining 90% are from known chronic diseases. If we assume that Emanuel's study applies to those at the end-of-life, then 1.4 million Americans each year have the frightening symptom of dyspnea; 1 million have pain.

In regard to the symptom of pain, 52% of these terminally ill patients had seen a primary care physician for the treatment of the pain in the previous 4 weeks and 20% had seen a pain specialist. Interestingly, 29% wanted more therapy and 62% wanted their therapy to remain the same. Several reasons for not wanting additional therapy were offered including fear of addiction, dislike of mental or physical side effects, and not wanting to take more pills or injections. This would suggest that, of the estimated 1 million dying Americans who have pain, 300,000 of them want more pain relief. Of the dying individuals, 700,000 of them may need more relief, but are not getting it because of the myth of opioid addiction or because their physicians do not know how to manage the adverse effects of pain-relieving therapies or do not know the various options that are available for pain relief.

We can turn our attention to the acute general hospital for a different sense of prevalence. In one study, 100 patients admitted to an acute palliative care unit in a U.S. teaching hospital were evaluated using a standardized data acquisition tool for the presence of physical symptoms during a 5-month period.⁷ Symptoms reported were fatigue in 81 patients, anorexia in 70, dyspnea in 61, xerostomia in 58, cough in 52, pain in 49, confusion in 37, depression in 37, constipation in 35, nausea in 30, insomnia in 23, and vomiting in 22. This is a population of whom 60% die within a week and all of whom have a prognosis of less than 6 months.⁸ This sample represents about 40% of all of the deaths in this particular hospital. Furthermore, these are patients who had received standard of care in the hospital, and were being transferred for further care. These data are similar to other data reported for a similar population.⁹

We can use this data to estimate the symptom

prevalence of patients who die in U.S. hospitals.¹⁰ We know that, in 2001, 50% of deaths from chronic illness occurred in U.S. hospitals. If we use the number of 2 million deaths, then about 1 million occurred in hospitals. If 40% of those hospital deaths are like those of patients from the general hospital described above, then 324,000 had fatigue, 280,000 anorexia, 244,000 dyspnea, 232,000 xerostomia, 208,000 cough, 196,000 pain, 148,000 confusion, 148,000 depression, 140,000 nausea, 92,000 insomnia in 23, and 88,000 vomiting.

We can conclude that despite standard health care, there remains a large burden of unrelieved symptoms. The population of patients who are experiencing these symptoms is growing because of the success of modern medicine.

Research need

Population-based measures of symptom prevalence and symptom relief. These will form the basis for population-based outcome assessments of the implementation of measures to relieve symptoms. Interinstitutional and regional comparisons could be possible as a quality measure.

HEALTH CARE PROFESSIONAL TRAINING TO RELIEVE SYMPTOMS

One explanation for unrelieved symptoms is that physicians, nurses, and other health professionals have not been trained to apply existing

knowledge. Although representative data are absent, one recent study stands out. A total of 3,227 oncologists answered a survey about their care of patients at the end of life. The methods were published as part of a report of the data as they relate to pediatric oncologists.¹¹ Table 1 summarizes their responses to the question about where they learned end of life care.¹²

The top sources of education are clear: trial and error and watching someone else. The problem, of course, is the someone else they are watching also learned by trial and error!

In 1997 the American Board of Internal Medicine (ABIM) identified End-of-Life Care as a required component for Internal Medicine training. In response, in 1998 Weissman and colleagues¹³ and Mullan and colleagues¹⁴ designed the National End of Life Residency Curriculum Project to help program faculty to develop curricula elements for their residency programs. As of 2004, this project had successfully recruited more than 400 training programs and more than 5000 residents and faculty to participate. Each residency program administered three quantitative instruments to its residents and teaching faculty: (1) a survey of concern, (2) a survey of confidence, and (3) a knowledge examination.

The results of the surveys of confidence and concern are shown in Figure 1. Respondents at various years of training rate their confidence and concern on a scale from one (least) to four (most). As might be expected, confidence increases across the years, whereas concern decreases.

In contrast, the results of the knowledge test are shown in the following graph where percent

TABLE 1. RESPONSES OF ONCOLOGISTS ABOUT SOURCES OF END-OF-LIFE CARE TRAINING

<i>From which of the sources listed below did you learn about delivering care to terminally ill patients?</i>	<i>Yes</i>	<i>No</i>
From formal courses in medical school	10%	85%
From clinical clerkships during medical school	27%	69%
From a role model during medical school	31%	64%
From a role model during internship and residency	56%	40%
From lectures during oncology fellowship training, radiation residency or surgical residency	33%	63%
From a role model during oncology fellowship training radiation residency or surgical residency	71%	26%
From a rotation on palliative care service or hospice	10%	85%
From trial and error during clinical practice	90%	8%
From colleagues during clinical practice	73%	23%
From a traumatic experience with a dying patient	38%	57%
From ASCO teaching sessions	10%	85%
From CME courses	17%	78%

ASCO, American Society for Clinical Oncology; CME, continuing medical education.

correct is charted versus year of training. End-of-life knowledge was essentially the same across all categories. Although the mean percent correct score for faculty (57.6% ± 14.0%) was slightly higher than that of residents (48.9% ± 13.3%), these differences are modest. The striking finding is how little the scores change, given the large differences in clinical experience and the self-reported confidence between faculty and residents.

The results of this research are clear. Although physicians develop confidence in end-of-life care, their knowledge does not change much. This is the first data that quantitates a widely observed phenomenon in physician education: the “arrogance—ignorance paradox.” With progressive years of training, physicians are more confident in their abilities, despite being no more knowledgeable.

Although large-scale surveys of nurse, social worker, and other health professional attitudes, knowledge, and skills have not been performed, small studies and inferences from studies of symptom control yield the same conclusion as for physicians.

This information helps put some of the prevalence data in perspective. We know that large numbers of Americans have uncontrolled symptoms at the end of life. One reason is that their health care professionals do not know how to apply the existing knowledge base.

- **Research Need:** To develop and test approaches to teach health care professionals evidence-based approaches to symptom control.

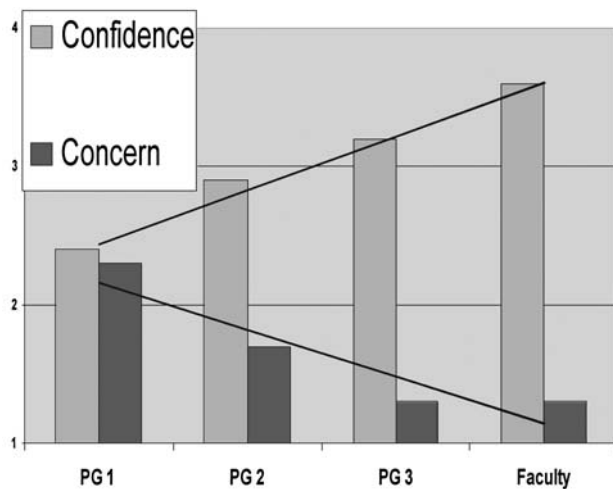


FIG. 1. Changing levels of confidence and concern among physicians regarding their ability to provide good end-of-life care. PG, physician group.

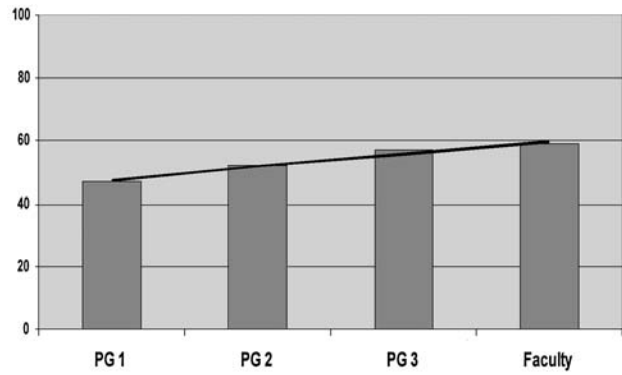


FIG. 2. Test scores of physician knowledge regarding end-of-life care. PG, physician group.

The evaluation of these educational initiatives need to include measures of routine behaviors, not just knowledge.

RELIEF OF SYMPTOMS

Another explanation for the high prevalence of symptoms is that the evidence base is missing. Large, well-designed, well-controlled studies of patients at the end of life have not been performed. When the size and scope of scientific studies for other human conditions is compared with this area, the difference is striking. There are a number of reasons for this. First, the thrust of medical research since the end of the 19th century has been to view symptoms as unimportant in themselves—they are interesting only insofar as they guide the astute clinician to a correct diagnosis. This fundamental principle has guided medical education and research for 150 years.¹⁵ When the disease is cured, the symptom will go away. What you do when the disease cannot be cured is not discussed and is certainly not researched. Second, this is a difficult population to study in a scientific manner. Patients are sick with multiple concurrent problems. The symptom under study is not the only variable. The exigencies of recruitment mean that patients with severe symptoms cannot be recruited to study because of their urgent distress.

Current clinical practice is guided by three major sources of information. First, data from other populations is applied. Let me give some examples. Gabapentin, an anticonvulsant used to prevent seizures, is widely used for neuropathic pain for patients near the end of life. Yet, the defini-

tive studies were performed with patients with post-herpetic neuralgia and diabetic polyneuropathy.^{17,18} Anticonvulsants as a group are widely advocated for the treatment of neuropathic pain. Yet, a Cochrane collaborative review of the field concluded that there are surprisingly few trials that show analgesic effectiveness. No trial compared different anticonvulsants. Only one study considered cancer pain; most studied trigeminal neuralgia. Although gabapentin is widely advocated, there is no evidence to suggest it is superior to carbamazepine.¹⁹ Benzodiazepines are widely used in patients near the end of life for treatment of insomnia and anxiety. Yet, there is no evidence from randomized controlled trials of benzodiazepines in palliative care.²⁰ Bisphosphonates are used to treat hypercalcemia and prevent bone-related events. Although there are descriptions of pain relief in patients with cancer, there is a need to define the most effective bisphosphonates and their relative effectiveness for different primary cancers near the end of life.²¹ Delirium is one of the most distressing symptoms in dying individuals; yet, there is insufficient evidence to draw any conclusions about the role of pharmacotherapy in terminally ill patients with delirium.²² Ketamine is one of the newest approaches to severe pain refractory to standard opioid therapy; yet, current evidence is insufficient to assess the benefits and harms of ketamine as an adjuvant to opioids for the relief of cancer pain.²³ Even something so basic to palliative care as opioid switching is supported by evidence that is largely anecdotal or based on observational and uncontrolled studies.²⁴

This summary of data has a direct relationship with the list of prevalent symptoms from the first section of this paper.³ Despite hundreds of thousands of Americans with these symptoms, the scientific evidence base is weak. For example, one study that showed that one of the main reasons that terminally ill patients at home did not want more pain therapy was the side effects of agents such as opioids. Switching opioids is advocated by experts as one of the main approaches to manage such side effects. Yet, there is no solid evidence base for the practice.

Second, results from small series (10–20 patients) of terminally ill patients near the end of life in single institutions are the best available evidence for the majority of symptoms in the population of interest.^{25–27} The reasons for this are many. Patients at the end of life represent a vulnerable population. In addition, usual scientific

approaches demand that the item under study be the only variable. Yet, patients at the end of life have, by definition, multiple variables in their pathophysiology, polypharmacy, and psychosocial–spiritual domains. Not the least important reason for small studies is the lack of funding for large multisite studies that have been the mainstay of progress in cancer, cardiology, pulmonology, and dementia research.

Third, and most influential of the three, are the application of anecdote and hearsay that was characteristic of medical practice before the 20th century. People do what they have heard other people say they do. For example, BRD (“bird”) suppositories (combinations of Benadryl, Reglan and Decadron) are popular throughout the country to control nausea in terminally ill patients at home. There are no data to drive this—just the anecdote that it works. Of course, we remember the perils of medicine by anecdote. The bleeding of General George Washington for epiglottitis is but one famous example.

The result is highly variable practice. For example, in a recent survey of experts regarding intravenous dosing of opioids for breakthrough pain, the authors found a 10-fold variation in dose and a 6-fold variation in timing interval.²⁸ A search through published sources was conducted, mirroring a wide range of combinations regarding recommendations for both the *prn* narcotic doses and the appropriate intervals at which they should be repeated in the event of continued pain. Data from 21 review articles and texts that provide guidelines for the treatment of cancer pain provided a 20-fold variation in recommended narcotic doses (1–20% of daily doses) and scattered opinions, or no direction, regarding appropriate dose intervals for potential repeat doses.

- **Research Need:** Well-powered, definitive studies of both existing and new approaches in terminally ill patients with the most common symptoms. A table listing basic and clinical research priorities in symptom control research are listed in Table 1–3 in the Institute of Medicine’s recent report is a place to start.²⁹

SYSTEMS THAT MAKE SYMPTOMS BETTER OR WORSE

Yet another reason for the high prevalence of unrelieved symptoms at the end-of-life is that existing knowledge is not being translated into

practice. We know that knowledge makes its way into practice when the system facilitates it.

A recent study makes this strikingly apparent. Surviving family members from a representative sample of U.S. deaths was surveyed about the care the decedent received in the last place of care. Hospital, nursing home, and hospice care settings were included.

As shown in Figure 3, patients cared for by hospice programs had better pain control than those cared for in hospital, nursing home, or home health systems.³⁰ Yet, the evidence base upon which all of these systems draws is the same. The data illustrate that there is something about the system that is different among these four settings. Exactly what hospice programs do that is different from other settings is unknown. Hospice programs report that a patient-centered, multidisciplinary team approach is what yields these results. No prospective randomized data are available to independently confirm this; but there should be no doubt that something different must explain this extraordinary variation. Interestingly, in this study, the rate of control of shortness of breath was about the same in all settings. This is a symptom for which there is almost no large scale research—yet it is one of the most prevalent symptoms for terminally ill patients at home.²

Another question from this extensive representative sample of U.S. deaths was the degree to which the family would rate the end-of-life care as “excellent.” This is shown in Figure 4.

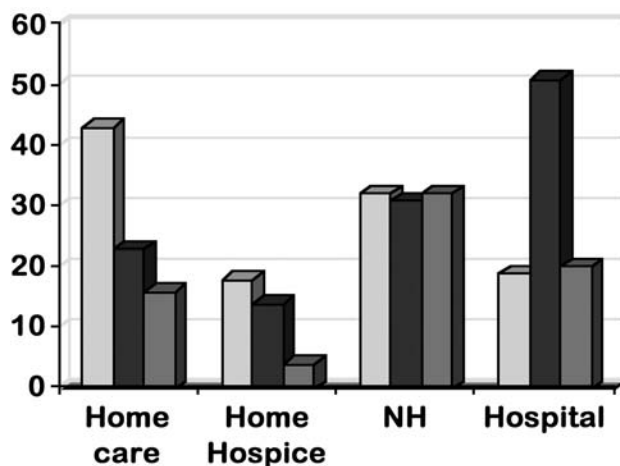


FIG. 3. Degrees of wanting more pain relief (bars with light shading), more physician contact (bars with medium shading), and wanting more respect (bars with dark shading) reported by surviving family members in various health care settings where the patient died. NH, nursing home.

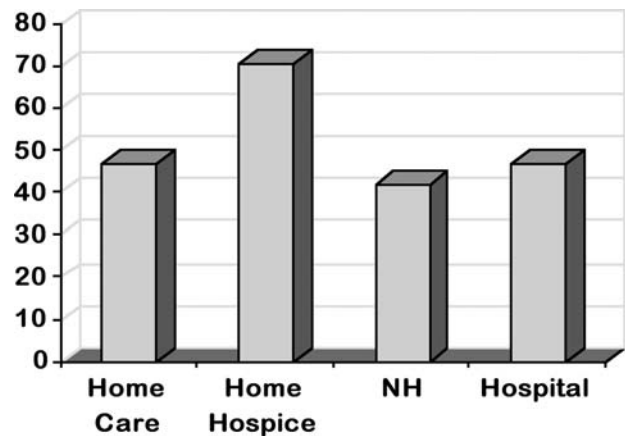


FIG. 4. Degree to which family, rated end-of-life care as “excellent” (shaded bars) in various care settings. NH, nursing home.

It should be clear that, in addition to better pain control, hospice programs which specialize in end-of-life care are rated as much better than the other settings for overall excellent care.

- **Research need:** To define the health care system interventions that are effective so that they can be broadly applied to the care of all individuals in the U.S.

SUMMARY

In summary, the prevalence of symptoms at the end-of-life in the US is high. Using existing data, we can estimate that 1.4 million persons in this country die with dyspnea that is inadequately managed. There is good evidence that health care professionals, including physicians, do not apply the existing evidence base because they have inadequate education. The evidence base for the management of symptoms at the end of life is largely extrapolated from other populations or is drawn from small, single-institution studies and personal anecdotes. Finally, we have evidence of a strong system effect on symptom control. For reasons that are not entirely clear, symptom control and overall satisfaction with end-of-life care is higher among those who have hospice care.

REFERENCES

1. National Consensus Project for Quality Palliative Care: Clinical Practice Guidelines for Quality Palliative Care, Executive Summary. *J Palliat Med* 2004;7:611–627.

2. Lynn J, Nolan K, Kabcenell A, Weissman D, Milne C, Berwick DM; End-of-Life Care Consensus Panel: Reforming care for persons near the end of life: The promise of quality improvement. *Ann Intern Med* 2002;137:117-122.
3. Emanuel EJ, Fairclough DL, Slutsman J, Alpert H, Baldwin D, Emanuel LL: Assistance from family members, friends, paid caregivers and volunteers in the care of terminally ill patients. *NEJM* 1999;341:956-963.
4. Emanuel EJ, Fairclough DL, Slutsman J, Emanuel LL: Understanding economic and other burdens of terminal illness; the experience of patients and their caregivers. *Ann Int Med* 2000;132:451-459.
5. Weiss SC, Emanuel LL, Fairclough DL, Emanuel EJ: Understanding the experience of pain in terminally ill patients. *Lancet* 2001;357:1311-1315.
6. Slutsman J, Fairclough D, Botoroff DH, Emanuel LL, Emanuel EJ: Managing end-of-life care: Comparing the experiences of terminally ill patients in managed care and fee-for-service. *J Am Geriat Soc* 2002;56:2077-2083.
7. Ng K, von Gunten C: Symptoms and attitudes of 100 consecutive patients admitted to an acute hospice/palliative care unit. *J P Symptom Manage* 1998;16:307-316
8. von Gunten CF, Martinez J: A program of hospice and palliative care in a private, non-profit US teaching hospital. *J Palliat Med* 1:265-275.
9. Fainsinger R, Miller MJ, Bruera E, Hanson J, Maceachern T: Symptom control during the last week of life on a palliative care unit. *J Palliat Care* 1991;7:5-11.
10. Brown University Death Atlas: <http://www.chcr.brown.edu/dying/2001DATA.HTM>. Accessed November 26, 2004.
11. Hilden JM, Emanuel EJ, Fairclough DL, Link MP, Foley KM, Clarridge BC, Schnipper: Attitudes and practices among pediatric oncologists regarding end-of-life care results of the 1998 American Society of Clinical Oncology survey. *J Clin Oncol* 2001;19:205-212.
12. Emanuel LL, Ferris FD, von Gunten CF, Von Roenn J: *EPEC-O: Education in Palliative and End-of-life Care for Oncology. The EPEC Project.*™ Chicago: 2005.
13. Weissman DE, Mullan PB, Ambuel B, von Gunten CF: End-of-life curriculum reform: outcomes and impact in a follow-up study of Internal medicine residency programs. *J Palliat Med* 2002; 5: 497-506.
14. Mullan PB, Weissman D, von Gunten C, Ambuel B and Hallenbeck J: Coping with certainty: perceived competency vs. training and knowledge in end of life care [abstract]. *JGIM* 2000;15:40(Suppl).
15. McCaffery M, Ferrell BR: Nurses' knowledge of pain assessment and management: How much progress have we made? *J Pain Symptom Manage* 1997;14:175-188.
16. von Gunten CF, Ryndes T: The Academic Hospice. *Ann Intern Med* 2005.
17. Rowbotham M, Harden N, Stacey B, Bernstein P, Magnus-Miller L: Gabapentin for the treatment of postherpetic neuralgia: a randomized controlled trial. *JAMA*. 1998;280:1837-1842.
18. Backonja M, Beydoun A, Edwards KR, Schwartz SL, Fonseca V, Hes M, LaMoreaux L, Garofalo E: Gabapentin for the symptomatic treatment of painful neuropathy in patients with diabetes mellitus: A randomized controlled trial. *JAMA* 1998;280:1831-1836.
19. Wiffen P, Collins S, McQuay H, Carroll D, Jadad A, Moore A: Anticonvulsant drugs for acute and chronic pain. *The Cochrane Database of Systematic Reviews* 2000. Issue 3.
20. Hirst A, Sloan R: Benzodiazepines and related drugs for insomnia in palliative care. *Cochrane Database Syst Rev* 2001.
21. Wong R, Wiffen PJ: Bisphosphonates for the relief of pain secondary to bone metastases. *Cochrane Database Syst Rev* 2002(2).
22. Jackson KC, Lipman AG: Drug therapy for delirium in terminally ill patients. *Cochrane Database Syst Rev* 2004 (2).
23. Bell R, Eccleston C, Kalso E: Ketamine as an adjuvant to opioids for cancer pain. *Cochrane Database Syst Rev* 2003 (1).
24. Quigley C: Opioid switching to improve pain relief and drug tolerability. *Cochrane Database Syst Rev* 2004 (3).
25. Bruera E, Palmer JL, Bosnjak S, Rico MA, Moyano J, Sweeney C, Strasser F, Willey J, Bertolino M, Mathias C, Spruyt O, Fisch MJ: Methadone versus morphine as a first-line strong opioid for cancer pain: a randomized, double-blind study. *J Clin Oncol* 2004;22:185-192.
26. Bruera E, Sweeney C, Willey J, Palmer JL, Strasser F, Morice RC, Pisters K: A randomized controlled trial of supplemental oxygen versus air in cancer patients with dyspnea. *Palliat Med* 2003;17:653-659.
27. Bruera E, Driver L, Barnes EA, Willey J, Shen L, Palmer JL, Escalante C: Patient-controlled methylphenidate for the management of fatigue in patients with advanced cancer: a preliminary report. *J Clin Oncol* 2003;21:4439-4443.
28. Ryan M, Moynihan RJ, Loprinzi CL: As-needed morphine: Yes, but at what dose and at what interval? *J Clin Oncol* 2005;23:3849-3852.
29. National Cancer Policy Board, Institute of Medicine and National Research Council: Improving palliative care for cancer. Washington, DC: National Academy Press, 2001, pp. 34-35.
30. Teno JM, Clarridge BR, Casey V, Welch LC, Wetle T, Shield R, Mor V: Family perspectives on end-of-life care at the last place of care. *JAMA* 2004;291:88-93.

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