Update in Hospice and Palliative Care

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Introduction

THE GOAL OF THIS UPDATE in hospice and palliative care is to identify, summarize, and critique journal articles published (either electronically or in print) between January 1, 2008 and December 31, 2008 with the highest potential for impact on the clinical practice of hospice and palliative medicine. We began with a hand search of 21 leading medical journals (including general internal medicine and specialized journals that publish research about hospice and palliative medicine) as well as a keyword search in PubMed using the terms hospice and palliative care. We also hand-searched the Cochrane Database of Systematic Reviews¹ and reviewed the Fast Article Critical Summaries for Clinicians in Palliative Care (PC-FACS).² Articles were reviewed and ranked based on study quality, scientific merit, and potential for immediate impact on the field of hospice and palliative care. Input from nationally recognized leaders in the field was solicited during the selection and rating process. The purpose of this article is to inform clinicians across a broad range of topics so as to allow them to have the most up-to-date information on issues of symptom control, communication, prognostication, and program development. Changes to practice emerging from the articles are summarized in Table 1.

Communication

Wright AA, Zhang B, Ray A, Mack JW, Trice E, Balboni T, Mitchell SL, Jackson VA, Block SD, Maciejewski PK, Prigerson HG: Associations between end-of-life discussions, patient mental health, medical care near death, and caregiver bereavement adjustment. *JAMA* 2008;300:1665–1673.

Summary and main findings

Clinicians worry that discussing end-of-life issues may be distressing for patients. There is a paucity of literature examining the relationship between end-of-life discussions and the care patients receive. This study examined the association between end-of-life physician–patient discussions and the care patients received at the end of life. Secondary outcomes were patient psychological distress and quality of life and caregiver mental health and quality of life during bereavement.

The design was a prospective longitudinal cohort study of patients with advanced cancer and their caregivers. Patients

were recruited from outpatient clinics. They were at least 20 years old and had an informal caregiver. Patients and caregivers were excluded if either was unable to speak English or Spanish, refused to participate, or had dementia or delirium. Whether the patient had an end-of-life discussion with a physician was determined by asking the patient in the baseline interview: “Have you and your doctor discussed any particular wishes you have about the care you would want to receive if you were dying?” Patient mental health diagnoses,³ were also assessed in the baseline interview. The type of end-of-life care the patient received, including use of life-sustaining treatments and hospice services, was determined by chart review after the patient’s death. Caregivers were interviewed after the patient’s death to determine mental health, quality of life, and their assessment of the patient’s quality of life at the end of life.

The authors enrolled 332 terminally ill patient–caregiver dyads; 123 (37%) patients reported having an end-of-life discussion with their doctor. The patients died a median of 4.4 months after study enrollment. Propensity scoring was used to balance patient performance status, symptom burden, and survival time by site. End-of-life discussions were not associated with negative emotional states or mental health diagnoses for patients. Patients who reported discussions were more likely to prefer treatments focused on symptom control (85 versus 70%, $p < 0.001$). These patients were less likely to undergo resuscitation (1 versus 7%, $p = 0.02$) and were more likely to have hospice stays 1 week or more (66% versus 45%, $p = 0.03$). Bereaved caregivers rated the patients’ quality of life at the end-of-life worse if the patient received aggressive interventions and better if the patient received hospice. Caregivers of patients who received life-sustaining treatments were at higher risk of developing depression and had worse ratings of their own quality of life.

Strengths and limitations

The strengths of this study are its use of important and clinically relevant outcome measures, the fact that it was conducted at multiple geographically distinct centers, and the fact that it used propensity scoring to adjust for differences in the baseline patient characteristics, reducing the possibility that confounding could account for the association between

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the predictor and outcome variables.⁴ A limitation is the use of patient report to assess whether an end-of-life discussion occurred; patients who preferred a more palliative approach to end-of-life care may have been more likely to recall having end-of-life discussions. In addition, those patients who had a conversation may have been more likely to prefer a more palliative approach and fewer life-sustaining treatments, and these overall preferences for care are not included in the analysis.

Clinical bottom line

End-of-life discussions are associated with less aggressive medical care and better quality of life for patients and caregivers.

Robinson TM, Alexander SC, Hays M, Jeffreys AS, Olsen MK, Rodriguez KL, Pollak KI, Abernethy AP, Arnold R, Tulsky JA: Patient-oncologist communication in advanced cancer: Predictors of patient perception of prognosis. *Support Care Cancer* 2008;16:1049–1057.

Summary and main findings

Patients need to have a clear understanding of their prognosis in order to make decisions about their medical care, but physicians often have difficulty communicating prognosis in ways that patients clearly understand.⁵ The goal of this study was to identify factors in patient–physician communication that are associated with agreement about the chance of cure of the patient’s underlying disease.

The investigators analyzed audiotaped oncologist–patient encounters at two outpatient cancer clinics. Patients were identified as those who the oncologist “would not be surprised if the patient was admitted to an intensive care unit or died within 1 year.” Patients were blinded to the eligibility criteria. After the audiotaped encounter, oncologists and patients were asked to complete surveys assessing the patient’s chance of cure. Eleven response choices were given: 0% chance of cure, 1%–10% chance of cure, 11%–20% chance of cure, etc. The investigators compared the physician rating of chance of cure to that of the patient, and rated concordance as good, medium, or poor.

The investigators created a coding scheme to identify physician statements in the audiotaped encounters about test results, treatment modalities, or the patient’s prognosis and divided these statements into optimistic, pessimistic, or uncertain. Optimistic and pessimistic statements were further divided into statements about the past/present and the future. Coders who were blinded to the degree of physician–patient concordance in prognostic estimate applied the coding scheme to the audiotapes of the physician–patient dyads with good and poor concordance.

The oncologist and patient provided numeric estimates of the chance of cure for 187 audio-recorded conversations, 69 pairs with good physician–patient concordance and 72 with poor physician–patient concordance. In all of the poor concordance pairs, patients overestimated their chance of cure. Oncologists made optimistic statements in 85% of the encounters and pessimistic statements in 46% (the sum is greater than 100% because physicians could make both optimistic and pessimist statements in the same conversation). Statements of optimism (past/present or future) and statements

about uncertainty were not related to concordance about chance of cure. There was a significant association between statements of pessimism ($p < 0.006$) and pessimism about the future ($p = 0.015$) and good patient–physician concordance about chance of cure.

Strengths and limitations

The finding that including pessimistic statements in conversations with patients increases concordance about chance of cure is an easily understandable and specific “teaching point” that can be translated into action at patients’ bedsides. Overall this was a well-designed study, and appropriate analyses were conducted to adjust for clustering within physicians as well as patient demographics and disease type. In this case control design good and poor concordance encounters were compared and medium concordance encounters were not included in the analysis. It is unclear how including the “medium” concordance group might have changed the overall results.

Clinical bottom line

Clearly communicating pessimistic information may improve patients’ understanding of prognosis.

Symptom Control

Krantz MJ, Martin J, Stimmel B, Mehta D, Haigney MC: QTc interval screening in methadone treatment. *Ann Intern Med* 2009;150:387–395.

Summary and main findings

Methadone is often prescribed to palliative care patients, but recent studies have raised concern that methadone prolongs the QTc interval, putting patients at risk for torsades de pointes and death. The Center for Substance Abuse Treatment convened a panel including experts in electrophysiology, pain management, and epidemiology to summarize this evidence and create a practice guideline. The panel met to review the evidence and unanimously agreed upon a practice guideline. A writing group was appointed to draft the manuscript. Two reviewers with expertise in electrophysiology and cardiology searched the literature to identify all publications that addressed the cardiac effects of methadone. The article concludes that methadone is associated with QTc interval prolongation, torsades de pointes, and sudden death. The highest risk of QTc prolongation and torsades was at doses above 100 mg/d, however sudden cardiac death has been reported at doses as low as 29 mg/d. The manuscript presents five practice guidelines:

1. *Disclosure*: Inform patients of arrhythmia risk when prescribing methadone.
2. *Clinical history*: Ask patients about any history of structural heart disease, arrhythmia, and syncope.
3. *Screening*: Obtain a pretreatment electrocardiogram (ECG) for all patients to measure the QTc interval, and then a follow-up ECG within 30 days and annually. Additional ECGs should be done if the methadone dosage exceeds 100 mg/d or if patients have unexplained syncope or seizures.
4. *Risk stratification*: If the QTc is greater than 450 but less than 500, discuss potential risks and benefits with

patients and monitor more frequently. If the QTc greater than 500 ms, consider discontinuing or reducing the methadone dose, eliminating contributing factors, such as drugs that promote hypokalemia, or using an alternative therapy.

5. *Drug interactions:* Be aware of interactions between methadone and other drugs that possess QT prolonging properties or slow the elimination of methadone.

Strengths and limitations

There is controversy in the literature about how these guidelines should be followed,⁶ especially given that some studies do not show dangerous QTc interval prolongation, and there is no evidence that screening decreases mortality.^{7,8} It is difficult to determine how these guidelines should be applied in settings in which obtaining an ECG would be a considerable burden, for example in home hospice patients.

Clinical bottom line

Hospice and palliative medicine clinicians should be aware of the potential risk methadone-related QTc prolongation, torsades de pointes, and death but it is unclear how these guidelines should be implemented in patients with advanced disease.

Thomas J, Karver S, Cooney GA, Chamberlain BH, Watt CK, Slatkin NE, Stambler N, Kremer AB, Israel RJ: *Methylalntrexone for opioid-induced constipation in advanced illness*. *N Engl J Med* 2008;358:2332–2343.

Summary and findings

While oral and rectal regimens may effectively treat constipation due to opioids in many patients, they can at times be ineffective, burdensome, and have unpredictable results. The researchers conducted a 2-week double-blinded randomized, placebo-controlled trial followed by a 3-month open-label extension study to determine if the peripherally acting opioid antagonist methylalntrexone relieves opioid-induced constipation that is refractory to other laxatives. Subjects were drawn from 27 nursing homes, hospices, and palliative care centers in the United States and Canada; 133 patients with a terminal cancer or noncancer diagnosis were enrolled. They had been treated with opioid analgesics for at least 2 weeks, and had constipation, defined as having fewer than 3 bowel movements in the week prior to enrollment and no bowel movement in the 24 hours prior to enrollment or having no bowel movement for 48 hours prior to enrollment. Patients were required to have a stable laxative and opioid regimen for at least 3 days prior to enrollment; 99% were using a laxative at enrollment. Patients with a life expectancy less than 1 month were excluded. One hundred six patients completed the 2-week trial, and 31 of the 89 who began the open-label extension completed it.

Patients were randomized to receive subcutaneous methylalntrexone, 0.15 mg/kg, or an equivalent volume of subcutaneous placebo every other day. If the patient had not had at least three bowel movements after 8 days, the study drug dose or volume of placebo was doubled. During the 2-week trial, patients continued the laxative regimen they were on at enrollment. They were only permitted to take other laxatives

4 hours before or after receiving the study drug or placebo. At the end of the 2-week trial, patients in both arms were given the option to enter the 3-month open label extension. The primary outcome was whether or not participants had a bowel movement after receiving the study dose. Secondary outcomes were pain scores, opioid withdrawal symptoms, and adverse events. To evaluate safety, patients were followed for 30 days after their last study dose.

Forty-eight percent of patients receiving methylalntrexone had a bowel movement within 4 hours after receiving the first study dose, compared to 15% of patients receiving placebo, $p < 0.001$. Pain and opioid withdrawal symptoms did not differ between the two groups. Most adverse events were mild and of the same frequency in both groups. Abdominal pain, flatulence, nausea, increased body temperature, and dizziness were more common in patients who received methylalntrexone. Similar results were found during the 3-month open label extension.

Strengths and limitations

That the authors performed a randomized double-blinded placebo controlled trial, which is often held as the highest standard of evidence, in a palliative care population is significant for the validity of the study results as well as the overall context of palliative care research. The use of rigorous methods to inform the clinical care of palliative care patients is a marker of the evolution of the field and research within it. Another strength is the inclusion of patients with varied terminal diagnoses from different types of care settings (except home/outpatient). Although almost all study patients were treated with other laxatives before and during the trial, the doses of the other agents is not reported. It is possible that aggressive titration of other laxatives could have similar effectiveness to methylalntrexone. The burdens of methylalntrexone treatment are its subcutaneous route of administration and its cost (\$50 per dose⁹), both of which could limit its use in outpatient, home, and hospice settings.

Clinical bottom line

While methylalntrexone may provide relief for patients with opioid-induced constipation refractory to other laxatives, its subcutaneous route of administration and cost may be limiting.

Akl EA, Barba M, Rohilla S, Sperati F, Terrenato I, Muti P, Bdair F, Schünemann HJ: *Anticoagulation for the long term treatment of venous thromboembolism in patients with cancer*. *Cochrane Database Syst Rev* 2008;CD006650.

Summary and findings

Hospice and palliative care patients with cancer are at increased risk for venous thromboembolism. This Cochrane Review compares the efficacy and safety of low molecular weight heparin (LMWH) to vitamin K antagonists for secondary prevention of deep venous thrombosis (DVT) and pulmonary embolism (PE) in patients with cancer. The authors performed a systematic review and meta-analysis of randomized, controlled trials. Six studies were identified that randomly allocated a total of 1661 outpatients with cancer and a radiologically confirmed DVT or PE to LMWH or oral anticoagulants. Five of the studies excluded patients younger

TABLE 1. RECOMMENDATIONS FOR CLINICAL HOSPICE AND PALLIATIVE CARE PRACTICE
EMERGING FROM ARTICLES PUBLISHED IN 2008

<i>Recommendation</i>	<i>Reference</i>
Start	
Encouraging oncologists to include statements of pessimism in conversations about prognosis; they improve patients' understanding of their chance of cure.	Robinson et al. ¹¹
Using change in functional status as predictor of outcomes for older patients.	Boyd et al. ¹²
Consider	
Getting ECGs on patients before and during methadone therapy.	Krantz et al. ¹³
Using methylnaltrexone to treat opioid-induced constipation that is refractory to other laxatives.	Thomas et al. ¹⁴
Using long-term LMWH to prevent recurrent DVTs and PEs in cancer patients.	Akl et al. ¹⁵
Continue	
Having conversations about goals of care with patients; they improve outcomes for both patients and their caregivers.	Wright et al. ¹⁶
Providing massage therapy to patients who want it; it is safe and may improve pain and mood in the short term.	Kutner et al. ¹⁷
Providing palliative care consultations to seriously ill hospitalized patients; they reduce hospitalization costs.	Morrison et al. ¹⁸

ECGs, electrocardiograms; LMWH, low molecular weight heparin; DVTs, deep venous thrombosis; PEs, pulmonary embolisms.

than 18 years of age, two excluded patients with life expectancy less than 3 months, and one excluded patients with poor functional status. The primary outcome was all-cause mortality during the follow-up period. Secondary outcomes were symptomatic recurrent DVT or PE during the follow-up period, major and minor bleeding, and thrombocytopenia.

There was no significant difference between LMWH and vitamin K antagonists for any of the evaluated mortality outcomes. Patients treated with LMWH were less likely to get a recurrent DVT or PE than patients treated with vitamin K antagonists, with 14% of patients who received oral anticoagulants getting DVTs or PEs during the follow-up period compared to 7% of those treated with LMWH (risk ratio = 0.51; 95% confidence interval = 0.35–0.74). There was no significant difference between LMWH and vitamin K antagonists for major or minor bleeding or thrombocytopenia.

Strengths and limitations

The review and meta-analysis are of high methodological quality, though the authors note that the quality of evidence was low for mortality and only moderate for recurrent venous thromboembolism. The subcutaneous route of injection and cost of LMWH may present a burden to some patients and hospices. The estimated cost of 1 month of LMWH is \$3600 compared with only \$14 for warfarin.¹⁰ Based on the data presented in the review, \$50,000 would be spent to prevent a recurrent DVT or PE in one patient. Further, these results may not be generalizable to many hospice and palliative care patients, as patients with life expectancy less than 3 months and poor functional status were excluded from some of the primary studies used for the meta-analysis.

Clinical bottom line

LMWH heparin is superior to vitamin K antagonists for preventing recurrent DVTs and PEs but does not reduce mortality.

Kutner JS, Smith MC, Corbin L, Hemphill L, Benton K, Mellis BK, Beaty B, Felton S, Yamashita TE, Bryant LL, Fairclough DL:

Massage therapy versus simple touch to improve pain and mood in patients with advanced cancer: A randomized trial. Ann Intern Med 2008;149:369–379.

Summary and main findings

Many patients with advanced disease seek massage therapy for relief of pain and other symptoms. The authors conducted a prospective randomized single blinded trial to assess the benefits of massage therapy on pain and others symptoms. Participants were English-speaking adults with advanced cancer (stage III or IV) who were enrolled at 15 hospices across the country. Eligible participants had at least moderate pain (≥ 4 on a 10-point scale) in the weeks before study enrollment. Participants were randomized to either massage therapy or simple touch. A licensed massage therapist who had at least 6 months of experience treating patients with advanced cancer performed the massage intervention. The simple touch control was designed to control for the time, attention, touch, and healing intent.

Pain was assessed immediately after the treatments and weekly for 3–4 weeks. Secondary outcome measures included changes in mood, heart and respiratory rates, quality of life, physical and emotional symptoms, analgesic medication use, and adverse events. The investigators defined changes in pain scores that would be considered clinically significant prior to analysis.

Overall 380 individuals were randomized: 188 to massage and 192 to control. Each group received a mean of 4 treatments. There was a clinically significant reduction in pain scores immediately after the treatment as compared to the patient's baseline, but not in the massage group compared to the control group. There were no clinically significant differences in the sustained pain outcomes. For the secondary outcome of change in mood, both groups improved compared to their baseline, and massage was statistically superior to simple touch. There were no between-group clinically significant differences in heart and respiratory rates, emotional and physical symptoms, quality of life, analgesic use, or adverse events.

Strengths and limitations

This is the largest study to date examining the effects of massage therapy on hospice patients with advanced cancer. The design is a randomized single-blinded controlled trial. There was no usual care control group, though the authors mention that the number of patients needed to power a study with three arms (massage, simple touch, usual care) would not be feasible given its costs. Another limitation is that the immediate postintervention pain assessment was performed by the therapist delivering the treatment and thus was not blinded. Assessors of the sustained measures were blinded to the patient's treatment allocation.

Clinical bottom line

Massage may have immediately beneficial effects on pain and mood among patients with advanced cancer, and is not associated with adverse events. Given the lack of sustained effects of massage and the observed improvement in both the massage and simple touch groups, simple touch interventions may also improve patient's quality of life.

Prognostication

Boyd CM, Landefeld CS, Counsell SR, Palmer RM, Fortinsky RH, Kresevic D, Burant C, Covinsky KE: *Recovery of activities of daily living in older adults after hospitalization for acute medical illness.* *J Am Geriatr Soc* 2008;56:2171–2179.

Summary and findings

Prognostication in the frail elderly presents a challenge for hospice and palliative medicine clinicians, patients, and caregivers. The goal of this study was to describe mortality and functional outcomes for older patients in the year after hospital discharge. The authors performed a secondary data analysis of two randomized-controlled trials that took place at a tertiary care center and a community teaching hospital between 1993–1998. This secondary data analysis included 2279 patients who survived to hospital discharge and were not completely dependent in activities of daily living (ADLs) at baseline. At the time of hospital admission, patients or their surrogates were asked to recall their baseline independence in each of five ADLs 2 weeks before admission. Patients' vital and functional status was assessed by interview at hospital discharge and 1, 3, 6, and 12 months.

Patients who were discharged with new or additional disability had higher mortality and worse function than those who were discharged at their baseline level of function. Forty-one percent of patients with new or worsening disability were deceased at 1 year, and less than one third of patients discharged with worse than baseline function returned to their baseline level of function. When patients did return to their baseline level of function, it was within the first month of hospital discharge 62% of the time. For patients who were discharged from the hospital at their baseline level of function, 67% maintained the same level of function for 1 year.

Strengths and limitations

These data demonstrate a strong relationship between function and mortality, and provide a way to associate func-

tional decline with recovery and mortality in a way that may be easier for patients/families to comprehend. A potential limitation is that some key potential predictors (e.g., depressive symptoms, postdischarge physical therapy) were not available in this secondary data analysis.

Clinical bottom line

New or additional functional disability at hospital discharge is associated with mortality and prolonged disability in older patients.

Palliative Care Consultation

Morrison RS, Penrod JD, Cassel JB, Caust-Ellenbogen M, Litke A, Spragens L, Meier DE; *Palliative Care Leadership Centers' Outcomes Group*: *Cost savings associated with US hospital palliative care consultation programs.* *Arch Intern Med* 2008;168:1783–1790.

Summary and findings

While studies have shown that hospital-based palliative care programs reduce costs, past studies were conducted single sites and methodological concerns have been raised about bias in their results because of sampling procedures. This retrospective case control study used propensity score analysis of data from eight hospitals in the United States with mature inpatient palliative care consult programs to determine if these programs decrease the cost of hospital care for seriously ill patients. Data from 4908 patients who received a palliative care consult between 2002–2004 were propensity-score matched, based on age, gender, marital status, medical insurance, primary diagnosis, attending physician specialty, and comorbid illness, to 20,551 patients who did not receive a palliative care consult. Daily and total hospitalization costs for each patient were abstracted from hospital accounting systems, and costs were compared for the total hospitalization as well as care provided up to the time of the palliative care consult.

For patients who were discharge from the hospital alive, palliative care consultation saved \$2,642 per admission, $p = 0.02$. For patients who died in the hospital it saved \$6,896 per admission, $p = 0.001$. Daily costs for palliative care and usual care patients were the same until 24–48 hours after the palliative care consultation, at which point costs for the palliative care patients decreased and costs for the usual care patients continued to rise. The authors calculate that for a 400-bed hospital, adding a palliative care program to do 500 consults per year would save \$1.3 million.

Strengths and limitations

This is the largest study to date showing that palliative care consultation programs significantly reduce hospital costs. Its strengths are its multicenter design, inclusion of a diverse group of patients, hospitals, and palliative care consultation programs, and use of propensity scoring to reduce the likelihood that confounding accounts for the association between palliative care consultation and decreased costs.⁴ That savings began 1–2 days after the consultation may be indicative of a causative relationship. It is unlikely that patient and physician preference could account for the magnitude of the findings,

although these factors were not adjusted for in analysis. All of the included hospitals had mature palliative care consult programs. Future research should investigate which elements of a palliative care program are necessary for cost reduction and how long it takes for a new palliative care program to begin to decrease costs.

Clinical bottom line

Palliative care consultation reduces hospitalization cost for seriously ill patients.

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Author Disclosure Statement

No competing financial interests exist.

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