

Evidence for Improving Palliative Care at the End of Life: A Systematic Review

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Background: Many persons and their families are burdened by serious chronic illness in late life. How to best support quality of life is an important consideration for care.

Purpose: To assess evidence about interventions to improve palliative and end-of-life care.

Data Sources: English-language citations (January 1990 to November 2005) from MEDLINE, the Database of Abstracts of Reviews of Effects, the National Consensus Project for Quality Palliative Care bibliography, and November 2005 to January 2007 updates from expert reviews and literature surveillance.

Study Selection: Systematic reviews that addressed "end of life," including terminal illness (for example, advanced cancer) and chronic, eventually fatal illness with ambiguous prognosis (for example, advanced dementia), and intervention studies (randomized and nonrandomized designs) that addressed pain, dyspnea, depression, advance care planning, continuity, and caregiving.

Data Extraction: Single reviewers screened 24 423 titles to find 6381 relevant abstracts and reviewed 1274 articles in detail to identify 33 high-quality systematic reviews and 89 relevant intervention studies. They synthesized the evidence by using the Grading of Recommendations, Assessment, Development, and Evaluation (GRADE) classification.

Data Synthesis: Strong evidence supports treating cancer pain with opioids, nonsteroidals, radionuclides, and radiotherapy; dyspnea

from chronic lung disease with short-term opioids; and cancer-associated depression with psychotherapy, tricyclics, and selective serotonin reuptake inhibitors. Strong evidence supports multi-component interventions to improve continuity in heart failure. Moderate evidence supports advance care planning led by skilled facilitators who engage key decision makers and interventions to alleviate caregiver burden. Weak evidence addresses cancer-related dyspnea management, and no evidence addresses noncancer pain, symptomatic dyspnea management in advanced heart failure, or short-acting antidepressants in terminal illness. No direct evidence addresses improving continuity for patients with dementia. Evidence was weak for improving caregiver burdens in cancer and was absent for heart failure.

Limitations: Variable literature indexing for advanced chronic illness and end of life limited the comprehensiveness of searches, and heterogeneity was too great to do meta-analysis.

Conclusion: Strong to moderate evidence supports interventions to improve important aspects of end-of-life care. Future research should quantify these effects and address the generalizability of insights across the conditions and settings of the last part of life. Many critical issues lack high-quality evidence.

Ann Intern Med. 2008;148:147-159.

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Americans struggling with symptoms and disability often die of chronic illness, and improving care during this period is important (1, 2). About 30% of Medicare's expenditures arise in patients' last year of life, and outlays will increase as the population ages (3). Hospices serve most Americans dying of cancer and 10% of all others (3). More than 25% of hospitals had palliative care services in 2003 (4). Even with growing specialization in palliative medicine and geriatrics, generalist physicians will provide most services.

People tend to follow characteristic patterns of clinical and functional decline as they approach the end of life. The clinical course exemplified by cancer often ends with obvious decline in the last weeks or months (5). In contrast, organ system failure tends to cause long-term lack of reserve and intermittent serious exacerbations, making the timing of death unpredictable (6, 7). A third group marked by frailty and often dementia usually declines slowly (6–8, 8) (**Appendix Figure**, available at www.annals.org). Organizing our report around these 3 common trajectories, we systematically reviewed the literature to address the following questions posed by the American College of Physicians Clinical Efficacy Assessment Subcommittee:

1. What are the *critical elements* for clinicians to address when caring for persons coming to the end of life?
2. What do definitions of the *end of life* suggest about identifying patients who could benefit from palliative approaches?
3. What treatment strategies work well for *pain, dyspnea, and depression*?
4. What elements are important in *advance care planning* for patients coming to the end of life?

See also:

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Summary for Patients I-42

Web-Only

Appendix Tables

Appendix Figure

CME quiz

Conversion of graphics into slides

Audio summary

5. What elements of *collaboration and consultation* are effective in promoting improved end of life care?

6. What elements of *assessment and support* are effective for serving caregivers, including family, when patients are coming to the end of life?

METHODS

Objectives

We reviewed evidence for the National Institutes of Health (NIH) State-of-the-Science Conference on Improving End-of-Life Care in December 2004 and updated it through November 2005 to support guideline development by the American College of Physicians. In addressing the 6 questions posed by this report, we focused on the clinical problems and literature related to pain, dyspnea, and depression; advance care planning; continuity; and caregiver concerns because they are especially important to patients and families (9). We focused on cancer, chronic heart failure, and dementia to illustrate differences in patient and caregiver experiences in the 3 characteristic trajectories of clinical and functional decline (5–8).

Literature Search

National Library of Medicine librarians searched MEDLINE for English-language publications (January 1990 to April 2004), and 1 reviewer used the Database of Abstracts of Reviews of Effects to search for reviews on cancer, congestive heart failure (CHF), and dementia. We added citations identified by the National Consensus Project for Quality Palliative Care (10). An advisory panel and peer reviewers suggested additional references until September 2004. We updated the original search strategy through November 2005 and further updated the literature to January 2007 by using the American Academy of Hospice and Palliative Medicine literature surveillance (for example, Fast Article Critical Summaries for Clinicians in Palliative Care) and the Annual Update (available at www.aahpm.org/membership/pcfacs.html). We did not search gray literature because it did not contribute to a recent review of the effectiveness of palliative care teams (11).

Literature Selection and Abstraction

Eight reviewers familiar with palliative care formed topic-oriented, 2-person teams. We accepted English-language publications from the United States, Canada, Western Europe, Australia, and New Zealand. We included studies about the definition of end-of-life care. Advance care planning reports had to address process or outcomes for patients and families (not just clinicians). Continuity publications had to address relationships with providers over time (12). Informal caregiving articles excluded bereavement. We described spiritual care outcomes when reported with emotional well-being. We rejected studies that addressed only surgery, chemotherapy, radiotherapy, stents, lasers, and similar technical interventions or if they reported only physiologic, laboratory, or radiologic outcomes. We characterized articles by research de-

sign quality, study population, settings, intervention, and outcomes. Studies addressing several topics are included in each topic's section.

Several methods reduced bias and enhanced accuracy, and 1 reviewer screened each citation. Two experts in systematic reviews conducted a structured, implicit evaluation of the quality of reviews. For intervention studies, each reviewer completed a training set, and 1 principal investigator reviewed a random subset from each reviewer's citations and double-reviewed outlier sets. Reviewers discussed uncertain decisions, and we abstracted full articles in teams, coming to consensus after independent review. Two principal investigators reviewed abstractions from articles, and we used piloted, standard forms throughout.

Data Analysis

The variety of outcome measures and study designs required qualitative synthesis of the evidence. We evaluated the strength of evidence related to each of the 6 questions for each of the 3 clinical and functional trajectories (for example, cancer, CHF, and dementia) (5–8). We discuss specific interventions only for reports not previously covered in high-quality reviews. We rated the study design, quality, consistency, and directness in each domain according to the Grading of Recommendations, Assessment, Development, and Evaluation (GRADE) system, yielding ratings of the strength of evidence of high, moderate, low, or very low (13). In each area, we rated the overall evidence based on unique studies within each domain, qualitatively taking into account studies addressed by several reviews.

Role of the Funding Source

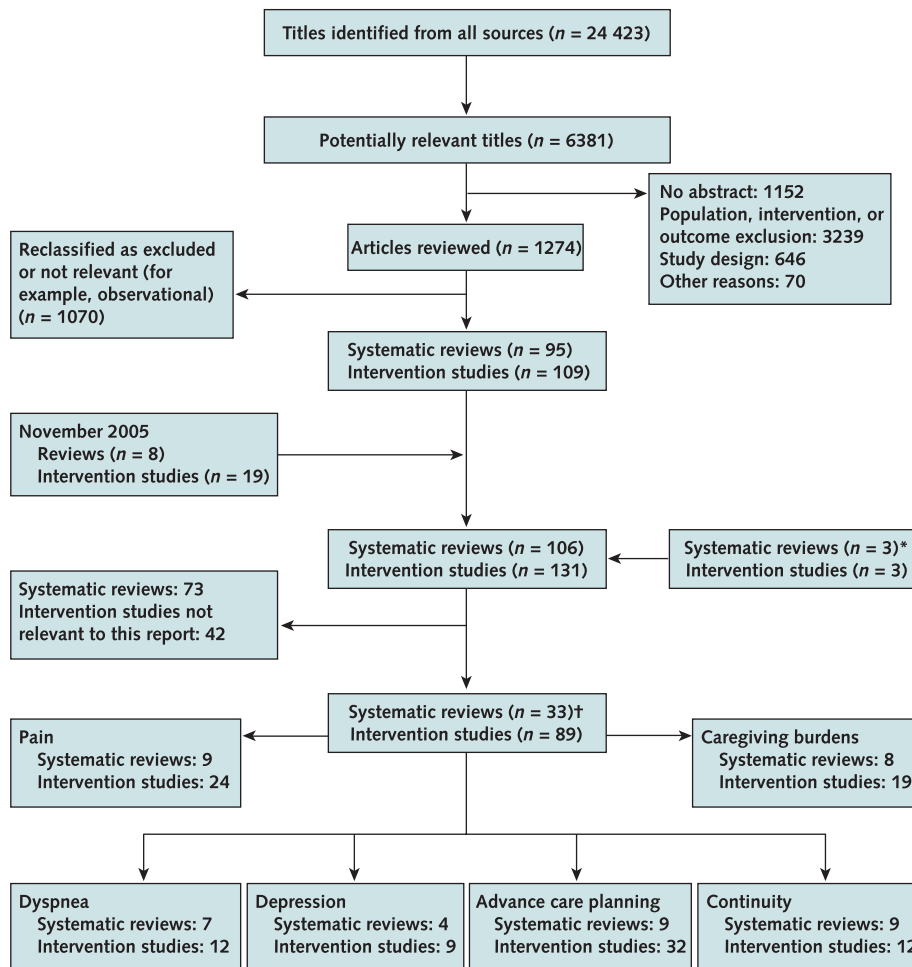
The Agency for Healthcare Research and Quality (AHRQ) and the National Institute of Nursing Research funded our initial systematic review. An advisory group from the National Institute of Nursing Research shaped our initial aims and review priorities. We complied with the methodological standards of the AHRQ and the National Institutes of Health Office of Medical Applications of Research (available at www.ahrq.gov/clinic/epcsums/eolsum.htm) (14). The funding sources played no role in the analysis of the data or decision to submit this material for publication. We produced this updated report under contract to the American College of Physicians Clinical Efficacy Assessment Subcommittee. This research did not involve human participants.

RESULTS

Literature Flow

The April 2004 search identified 24 423 titles, from which we identified 6381 potentially relevant abstracts and then 1274 potentially relevant articles. Accepted articles included 95 systematic reviews and 109 reports of interventions. The November 2005 update identified an additional 944 titles, including 8 systematic reviews and 19 reports of interventions. After November 2005, expert sources added an additional 3 systematic reviews and 3

Figure. Study flow diagram.



*From the American Academy of Hospice and Palliative Medicine Fast Article Critical Summaries for Clinicians in Palliative Care and Annual Updates, November 2006 to January 2007. †Some reviews and interventions were relevant to more than 1 domain.

interventions. This report includes 33 high-quality systematic reviews and 89 intervention reports (Figure). Appendix Tables 1 to 5 (available at www.annals.org) provide details about the literature cited.

What Are the Critical Issues for Clinicians to Address when Caring for Persons Nearing the End of Life?

Expert opinion and qualitative research have characterized priority concerns for patients in late life (15–19). One national survey defined whether patients, caregivers, and providers have similar concerns (15), and an after-death survey evaluated whether health care achieves these ends (20). Important topics include preventing and treating pain and other symptoms, supporting families and caregivers, ensuring continuity, making informed decisions, attending to emotional well-being (including spiritual concerns), sustaining function, and surviving longer. The studies addressed various illnesses and settings, showing that dying patients and their families generally share these concerns.

What Do Definitions of End of Life Suggest about Identifying Patients Who Could Benefit from Palliative Approaches?

The literature used various approaches to identify patients at the end of life. Some used clinician assessment of “active dying” or “patient readiness,” but no precise definitions or performance characteristics of these terms have been published. Many studies used specified clinical characteristics, survival prediction rules, or physician judgment (21). Although prognostic tools usefully characterize subpopulations (for example, heart failure), many patients with fatal conditions have substantial probabilities for 2- or 6-month survival, even in their last week of life (6, 7). Patients with metastatic cancer, who have an estimated 10% or greater chance of dying within 6 months, are more likely to prefer to avoid resuscitation, even when survival was much less likely than they acknowledged (22). Thus, clinicians might define the end of life as having a fatal condition, risking death with the next exacerbation, or be-

ginning to acknowledge the seriousness of the situation (23). Asking clinicians “Would it be a surprise if this patient were to die within 6 months?” is being used widely but also has had no rigorous testing (24). The studies emphasize that acknowledging death risk is important for decision making. Waiting for near-certainty would fail to identify most dying people, so palliative approaches need to be regularly incorporated for people living with serious illnesses.

What Treatment Strategies Work Well for Pain, Dyspnea, and Depression?

Pharmacologic and Complementary and Alternative Medicine Treatments for Pain

Nine systematic reviews focused on pain (25–33), of which 4 addressed cancer pain (26, 27, 30, 31) (Table and Appendix Table 1), and several addressed pharmacologic and complementary and alternative medicine treatments (28–31). Our update identified reviews of the efficacy of opioids in noncancer pain (32) and local anesthetics for neuropathic pain (33).

A methodologically robust review of cancer pain evaluated patients in randomized trials receiving nonsteroidals, breakthrough medications, spinal and other adjuvants, opioid trials, chemotherapeutic agents, external-beam radiation and radionuclides, alternative medicine, and bisphosphonates (for metastatic bone pain or painful complications, and most studies of breast cancer and also some studies including myeloma). Seventeen studies generally supported the use of nonsteroidals, opioids, bisphosphonates, and radiotherapy or radiopharmaceuticals. Heterogeneity of study design barred comparisons of specific opioids or opioid delivery strategies. The review also affirmed the effectiveness of neurolytic celiac plexus block for pain relief in visceral cancer (26). Two reviews found insufficient evidence on exercise or acupuncture (30, 31), and 2 reviews of complementary and alternative medicine approaches found varying effects, which were partly attributed to study heterogeneity and small numbers of participants (28, 29).

We identified 24 additional studies (of 23 pain interventions) (34–57) (Appendix Table 5). Most focused on cancer or cancer-predominant populations. Ten trials were randomized or controlled, with 9 targeting opioid delivery (36, 43, 44, 49, 50, 52–54, 56, 57) and 1 evaluating bisphosphonates (55). Others studies addressed heterogeneous interventions (for example, reflexology, aromatherapy, massage, exercise, and toileting) (38–40, 47). Randomized or controlled trials of pharmacologic or complementary and alternative medicine approaches added little to published systematic reviews.

Care Delivery Interventions for Pain

Among systematic reviews and meta-analyses of pain, 1 provided a meta-analysis of the effects of palliative care teams on pain (25) and 2 focused on the clinical organization of services (27, 29). Few studies in the review of multi-

disciplinary teams addressed hospital-based palliative care consultation services, whereas the rest addressed non-specialist physicians and nurses working in hospitals, nursing homes, and home settings. The review identified 43 studies, including 6 randomized studies (25). Twenty studies of team interventions found palliative care to be better than usual care (effect size, 0.13 [95% CI, 0.11 to 0.63]). A review of supportive services for cancer (27) included 27 reports that addressed pain, many of which overlapped with the previous review. Mixed evidence supported clinical pathways, patient education, and massage.

Of the 24 additional studies of pain, we identified 9 intervention studies about service delivery (34, 35, 37, 41, 42, 45, 46, 48, 51), of which 4 were randomized, controlled trials (RCTs). Informal caregivers of patients receiving intensive palliative home nursing care just before death rated the patient’s pain as alleviated in after-death surveys (2.52 vs. 3.00 on a 4-point scale; $P < 0.050$) (41, 42). A cluster-randomized trial of hospital-based palliative care collaborating with community-based primary care providers did not improve the European Organization for Research and Treatment of Cancer Quality-of-Life Questionnaire C30 pain scores (45). Compared with the positive findings of the review of multidisciplinary teams (25), 1 study randomly assigned outpatient clinics for palliative care team consultation. Participants with chronic obstructive pulmonary disease (COPD), CHF, and cancer (50 intervention, 40 control) had no benefit on several pain items (from the Brief Pain Inventory) (37). Another intervention provided quality-of-life feedback to clinicians during a visit and did not change pain on the Short Form-36 Health Survey (48).

Strong evidence from consistent randomized trials supports treating cancer pain with nonsteroidals, opioids, radionuclides, and radiotherapy. Less consistent evidence supports the use of bisphosphonates for pain. Weak evidence, mostly from nonrandomized designs in cancer-predominant populations, supports multidisciplinary teams. No evidence addressed pain management in advanced heart failure or dementia. Although a recent review demonstrated the efficacy of opioids for noncancer pain (32), opioid use is controversial in noncancer pain (58).

Palliative care services are becoming common, although their effectiveness is not well tested. Small studies suggest that pain is common and severe in advanced noncancer conditions (59, 60). Thus, research priorities should address pain in advanced noncancer conditions and service delivery strategies generally.

Pharmacologic and Complementary and Alternative Medicine Treatments for Dyspnea

Seven systematic reviews addressed dyspnea (27, 28, 61–65), of which 3 addressed COPD (62, 64, 65) and 3 addressed mixed diseases (28, 61, 63) (Table and Appendix Table 1). Twelve additional reports of interventions

Table. Summary of Systematic Reviews and Additional Intervention Studies of Palliative and End-of-Life Care*

Domain	Literature Identified†	Summary of Evidence and GRADE Rating‡
Symptoms		
Pain	9 systematic reviews (25–33) and 24 reports of interventions (34–57)	Strong evidence supports approaches to treating cancer pain with nonsteroidals, opioids, radionuclides, and radiotherapy. Less consistent evidence supports use of bisphosphonates for pain or painful complications (for example, fracture). Weak evidence supports multidisciplinary teams. No evidence addressed pain management in advanced heart failure or dementia.
Dyspnea	7 systematic reviews (27, 28, 61–65) and 12 reports of interventions (37, 41, 42, 45, 46, 48, 57, 66–70)	Strong evidence supports treating dyspnea with β -agonists and opioid use in COPD, although these trials are small and short in duration. Weak evidence supports opioid use for relieving dyspnea in cancer. Strong evidence supports pulmonary rehabilitation and oxygen for improving symptoms during short-term exercise in COPD. Evidence for oxygen use in cancer is weak, and few studies address it. Weak evidence supports care delivery interventions for dyspnea. No evidence addressed symptomatic dyspnea management in advanced heart failure.
Depression	4 systematic reviews (26, 27, 30, 71) and 9 reports of interventions (35, 37, 39–42, 72–74)	Strong evidence supports psychotherapy, as well as tricyclic antidepressants and SSRIs, for depression treatment in cancer.
Advance care planning	9 systematic reviews (25, 29, 75–81) and 32 reports of interventions (35, 82–112)	Moderate evidence supports multicomponent interventions to increase advance directives; however, such studies seldom measure clinically important outcomes. Recent research supports care planning through engaging values, involving skilled facilitators, and focusing on key decision makers (for example, patients, caregivers, and providers).
Continuity	9 systematic reviews (25, 27, 29, 113–118) and 12 reports of interventions (103, 104, 112, 119–127)	Moderate evidence supports multidisciplinary interventions that target continuity to affect utilization outcomes. Evidence is strong for reducing readmissions in heart failure, but insufficient evidence was available for other conditions. Successful interventions involved multidisciplinary teaming, addressed patient needs across settings and over time, and facilitated communication by personal and technological means.
Caregiver burdens	8 systematic reviews (25, 27, 29, 129–133) and 19 reports of interventions (103, 104, 134–150)	Weak to moderate evidence suggests that caregiver interventions, especially when comprehensive and individually targeted, can improve various measures of caregiver burden, although effect sizes are small. Moderate evidence suggests that palliative care interventions improve caregiver satisfaction. Existing research has focused on dementia and, to a lesser extent, cancer.

* COPD = chronic obstructive pulmonary disease; GRADE = Grading of Recommendations, Assessment, Development, and Evaluation; SSRIs = selective serotonin reuptake inhibitors.

† Appendix Tables 1 to 5 (available at www.annals.org) describe details of individual studies and the overlap of studies included in the various systematic reviews.

‡ The GRADE standards rate evidence by considering 4 attributes of available literature: study design, study quality, consistency or similarity in the results of studies, and directness or relevance of the findings (13).

included dyspnea evaluation (37, 41, 42, 45, 46, 48, 57, 66–70) (Table and Appendix Table 5). Four reviews focused on pharmacology (61, 63–65), and a review of complementary and alternative medicine included several studies with dyspnea outcomes (28).

One review identified 34 randomized trials of oxygen for COPD, cancer, and CHF. Nine trials addressed the use of oxygen for long-term relief, with mixed results. Twenty of 22 studies in COPD showed either improved endurance or reduced dyspnea with oxygen for short-term relief with exercise. Three small studies in cancer showed improvement, although 1 found oxygen equivalent to room air (63). A review of randomized trials testing at least 4 weeks of rehabilitation for COPD identified 12 trials with reduced dyspnea (effect size, 0.62 [CI, 0.35 to 0.89]). Lower-extremity training enhanced effective rehabilitation (62).

A review of opioids for dyspnea in advanced lung disease identified 18 double-blind, randomized studies. Twelve trials addressed COPD, and 2 addressed cancer. Meta-analysis of 13 studies showed benefit (effect size,

−0.31 [CI −0.50 to −0.13]). Nebulized and oral opioids were equivalent. Constipation, nausea, and vomiting were the most common side effects. Four studies measured arterial blood gases, and 9 measured oxygen saturation. One study found a significant but clinically trivial increase in PCO_2 during treatment with dihydrocodeine (61). Of the other relevant reviews, 1 review of 33 unique RCTs demonstrated the effectiveness of β -agonists (65). Few studies of theophylline evaluated dyspnea as an outcome (64), and weakly designed complementary and alternative medicine studies demonstrated conflicting results (28).

Twelve additional studies (11 unique interventions) explored treatments for dyspnea, and these studies focused on several diseases in which dyspnea is prominent (37, 41, 42, 45, 46, 48, 57, 66–70). Three studies (2 RCTs) focused on cancer (46, 48, 66), and 2 more RCTs focused on cancer-predominant hospice patients (41, 42, 45). Two RCTs targeted heart failure (67, 70) and COPD, respectively (68, 69), and 1 controlled clinical trial targeted all 3 conditions (37).

Additional studies tested various clinical interventions. Two studies focused on oxygen and morphine in cancer and COPD (66, 68), 1 evaluated acupuncture in COPD (69), and 2 assessed exercise and inspiratory muscle training for CHF (67, 70). Two of these studies were randomized. In the first 33 nonhypoxemic patients (31 with advanced lung cancer), oxygen did not improve 6-minute walk distance, dyspnea, or fatigue (66). A randomized, double-blind, placebo-controlled crossover study of morphine in 48 patients, 42 of whom had COPD, showed less dyspnea on a visual analogue scale, both in the morning (-6.6 mm [CI, -1.6 mm to -11.6 mm]) and in the evening (-9.5 mm [CI, -3.0 mm to -16.1 mm]), as well as improved sleep (1 vs. 8 dyspnea-related awakenings). Despite routine use of laxatives, constipation worsened, and 1 patient discontinued morphine because of sedation. Patients had no adverse respiratory outcomes (68).

Care Delivery Interventions for Dyspnea

A review of supportive cancer services identified many studies, but only 6 measured dyspnea. Two randomized trials showed improvement with nurse-led patient training in coping techniques, including relaxation (27).

The 6 additional intervention studies of dyspnea that addressed care delivery interventions evaluated 5 service delivery models (37, 41, 42, 45, 46, 48). Of the randomized studies, 1 project randomly assigned 2 general medicine clinics to palliative care interventions for chronic lung disease and CHF (85% of patients with dyspnea). Intervention patients were more often breathing comfortably (odds ratio, 6.07 [CI, 1.04 to 35.56]), and physical limitations due to dyspnea improved for intervention patients and worsened among control patients (37). Facilitated patient-provider communication did not improve physical symptoms (48). Two randomized interventions, 1 of intensive palliative home nursing care just before death from cancer and another of consultation with community-based providers for patients with cancer, showed no impact on dyspnea, although evaluation of dyspnea was very limited (41, 42, 45).

Strong evidence from consistent, high-quality RCTs supports treating dyspnea with β -agonists, and strong evidence from small but high-quality RCTs of short duration supports opioid use in COPD. Weak evidence supports opioid use for relieving dyspnea in cancer. Strong evidence from consistent, moderate-quality RCTs supports pulmonary rehabilitation, and consistent evidence from RCTs supports the use of oxygen for improving symptoms during short-term exercise in COPD. Evidence for oxygen use in cancer is weak, and few studies address it. Weak evidence from few studies with mixed results support care delivery interventions for dyspnea. No evidence addressed symptomatic dyspnea management in advanced heart failure. Strengthening the evidence base for dyspnea management

in cancer and heart failure is particularly critical because dyspnea is common in these conditions.

Pharmacologic and Complementary and Alternative Medicine Treatments for Depression

Four reviews addressed depression or mood, and all focused on cancer (26, 27, 30, 71) (Table and Appendix Table 1). We identified an additional 9 reports about interventions to improve depression or mood (35, 37, 39–42, 72–74) (Table and Appendix Table 5). Reviews of guided imagery and exercise identified a few studies with mixed results on mood in cancer (30, 71).

One methodologically robust review identified 11 controlled trials of antidepressants and 1 trial of pain and depression treatment in cancer. Tricyclic antidepressants and selective serotonin reuptake inhibitors were uniformly effective, given sufficient treatment duration (that is, ≥ 6 weeks). This review also found strong, consistent efficacy from RCTs of various psychosocial interventions (that is, education, cognitive and noncognitive behavioral therapy, informational interventions, and individual and group support) (26).

Nine additional reports (8 interventions, including 3 randomized trials focused on care delivery innovations) addressed depression or existential well-being (35, 37, 39–42, 72–74). Seven of these focused on cancer, and only 2 focused on noncancer populations (37, 72). Of those addressing clinical interventions, 3 addressed aromatherapy (39, 40, 73), and 1 addressed antidepressants and antipsychotics in inpatients with dementia (72).

Care Delivery Interventions for Depression

A review of supportive cancer care identified studies that addressed social and spiritual support. Among diverse studies examining depression outcomes, behavioral interventions were generally effective, but evidence was mixed about delivery system interventions (27).

Four additional interventions reported service innovations (35, 37, 41, 42). Of these, a randomized trial of palliative outpatient care for previously treated patients with depression found no effect on depression, although spiritual well-being (evaluated with a 20-item scale) improved only for intervention patients (37). Two methodologically limited randomized trials of a portable health record and intensive home care support, mostly of patients with cancer who were very near death, did not change depression (35, 41, 42). A before-and-after study of “dignity therapy,” which included psychotherapy and facilitated life recall, improved both existential and emotional well-being (74).

When depression has been identified, strong evidence from several high-quality RCTs supports psychosocial interventions to treat depression in cancer. Although derived from fewer studies, RCTs consistently support tricyclic antidepressants and selective serotonin reuptake inhibitors for treating depression in cancer when treatment lasts 6 weeks

or longer. Critical gaps include that the evidence base does not address late-stage cancer (for example, terminal care) or delivery system changes. Existing evidence does not support palliative care delivery interventions. No evidence addressed depression management in advanced heart failure or dementia.

What Issues Are Important in Advance Care Planning for Patients Approaching the End of Life?

Nine systematic reviews addressed establishing goals of care and advance care planning (25, 29, 75–81), and 32 additional reports addressed interventions to improve advance care planning (35, 82–112) (Table and Appendix Tables 1 and 2). An older review (10 randomized trials) found inconclusive evidence for whether conveying bad news improved short-term patient knowledge, psychological adjustment, and satisfaction (75). One review concluded that multicomponent interventions yield more advance directives than limited strategies do. An older review measured similar conclusions (76), and 10 RCTs since 1997 compared advance directive delivery methods (79). Seven studies (4 RCTs) evaluated effective outcomes of advance care planning: None found harms, and 2 were positive (78). A systematic review of factors influencing death at home found 58 observational studies, and the expression and recording of preferences for dying at home was strongly associated with that outcome in the 15 highest-quality studies (80). A recent review found that patient and surrogate preferences were often concordant (an average of 68% in 16 studies involving 19 526 paired responses) (81).

Two reviews addressed utilization outcomes. Nurse-facilitated decision making; ethics consultation; and family, provider, and patient communication interventions reduced end-of-life care use in intensive care (77). A meta-analysis of palliative care teams' effects identified 9 mostly observational studies that suggested more frequent death at home with palliative care (effect size, 0.28 [CI, 0.11 to 0.71]). The significance of this effect, however, depended on inclusion of the National Hospice Study, a large demonstration of hospice care from 25 years ago, which may not reflect current practices (25).

We found 32 additional studies (30 interventions, with 13 randomized trials) related to goals of care and advanced care planning (35, 82–112). Four studies addressed relatively healthy outpatients; 15 addressed unspecified illnesses mostly in high-intensity settings; and the remainder addressed CHF, COPD, dementia, AIDS, and dialysis. Interventions in the highest-quality designs (RCTs or controlled clinical trials with randomization by provider or site) tested multidisciplinary decision making in a nursing home (86, 93), advance care planning workbook (94), peer mentoring (95), ethics team consultation (103, 104), preoperative structured care planning (98), nursing home quality improvement (105), and the effects of directives on mutual understanding (87). Several RCTs focused on ap-

proaches to increasing advance directive completion or surrogate-patient understanding (82, 89, 97, 107, 111, 112).

Six of the randomized studies tested skilled facilitators or goals clarification (86, 93, 94, 98, 103, 104). A study of 198 nursing home residents used goals-oriented interviews with conclusions communicated to nursing home physicians to increase hospice use from 1% to 20% ($P < 0.001$) (86). Documented treatment limitations and preference-concordant care increased for patients served by social workers experientially trained in care planning (93). Ethics team consultation reduced days in the intensive care unit (ICU) (-1.44 days; $P = 0.03$), hospital (-2.95 days, $P = 0.01$), and ventilator (-1.7 days; $P = 0.03$) without reducing length of life (103, 104). For patients with AIDS, a values-oriented program facilitated by social work ("Your Life, Your Choices" workbook) improved rates of physician discussion (64% vs. 38%; $P > 0.001$), living wills (48% vs. 23%; $P < 0.001$), and patient-provider and patient-caregiver understanding (94). A manual ("Respecting Choices") and nurse facilitator successfully promoted understanding among patients preparing for cardiac surgery (98). A controlled, quality improvement intervention in nursing homes increased hospice enrollment, pain management orders, and in-depth discussions about palliative care (105). Two nonrandomized, quality improvement interventions showed substantial effects with structured orders for dying hospitalized patients (110) and implementing a clinical pathway (109).

Moderate evidence suggests that multicomponent interventions increase advance directives. Although these studies seldom measure clinically important end points, expressed preferences are associated with death at home in observational studies. Recent research suggests that engaging values; involving skilled facilitators; and including patients, caregivers, and providers can increase the rates and effectiveness of communication about late-life goals and advance care planning. Many studies focused on settings in which a wide spectrum of serious conditions is typically represented (for example, ICU, hospital, and nursing home), underscoring that palliative care approaches are generally effective when patients are living with serious illnesses.

What Opportunities for Collaboration and Consultation Are Effective in Promoting Improved End-of-Life Care?

Nine systematic reviews addressed continuity (25, 27, 29, 113–118), including 1 largely subsumed by more recent reviews (115) and 1 discussed in the previous section (25) (Table and Appendix Table 1). One review focused on cancer, 2 on COPD, 3 on CHF, and 2 on palliative or end-of-life care. Our review identified 11 additional intervention studies (103, 104, 112, 119–127) (Table and Appendix Table 4).

A review of case management in end-of-life care identified 4 RCTs, with 2 that evaluated utilization, having mixed effects (29). A review of improved coordination for

supportive cancer care identified 9 RCTs of portable records (mostly negative) or palliative care–home care coordination (with mixed effects for patient, caregiver, and utilization) (27). A review of nurse care management for COPD found 9 RCTs, with 1 reporting reduction in readmission (113). A review and meta-analysis of intensive in-home support from respiratory care nurses teamed with hospital support for COPD (7 RCTs) showed reduced hospital days and costs but unchanged readmissions (114).

For CHF, a review identified 29 RCTs of multidisciplinary teams after hospitalization, which always reduced hospitalizations with team follow-up (relative risk, 0.81 [CI, 0.71 to 0.92]) or enhanced self-care (relative risk, 0.73 [CI, 0.57 to 0.93]). Telephone contact and advice reduced heart failure but not all-cause hospitalizations (116). Another review (15 RCTs) focused on interventions to reduce utilization or improve patient outcomes. Both reviews found improvement in half of the studies examining quality of life or functional status (116, 118). By pooling quality-of-life scores for 6 RCTs, 1 study reported a statistically significant improvement with after-hospital disease management (26% vs. 14%; $P = 0.01$) (117). Although studies typically excluded terminally ill persons, trials enrolled patients with advanced illness and substantial mortality rates (that is, approximately 5% to 20% 6- to 12-month mortality rates).

Twelve additional reports (11 interventions) addressed management and informational and relational aspects of continuity (103, 104, 112, 119–127). These reports include 3 RCTs or controlled clinical trials addressing heart failure (120, 122, 125) and 7 RCTs or controlled clinical trials (of 6 interventions) addressing mixed or other conditions, including frailty (103, 104, 112, 123, 124, 126, 127). Two were discussed in the previous section (103, 104). Intensive medication counseling in stable heart failure improved adherence and decreased edema and dyspnea (125). Results of 2 studies, 1 that used a nurse care manager and telephonic monitoring linked to an electronic scale and 1 that implemented a critical pathway for heart failure with staff education, video teleconferencing, and a hospital-based quality improvement program, were mixed (120, 122). Two RCTs provided team-based home care for frail elderly patients and thereby maintained function (123, 124). Three RCTs used care managers among seriously ill patients at risk for hospitalization. One trial reduced readmissions among at-risk inpatient discharges; a clinical pathway reduced admissions among residents with pneumonia; and palliative case managers increased advance directives and lowered utilization (112, 126, 127).

In summary, moderate evidence supports the ability of multidisciplinary interventions that target continuity to affect outcomes of utilization in advanced illness. Strong evidence derived from many high-quality RCTs shows that reducing readmissions and other inappropriate utilization in advanced heart failure is possible, and the evidence is more consistent among more comprehensive and multidis-

ciplinary approaches. Fewer robust studies addressed other specific conditions. Weak evidence addressed cancer (mostly in the palliative care literature), and no direct evidence was found for dementia. Successful interventions used multidisciplinary teams involving nurses and social services, ensured continuity across settings, and facilitated communication. Better understanding of how health care systems can improve continuity in cancer and dementia is needed. Multiple complex transitions are common in these and other advanced illnesses (128).

What Aspects of Assessment and Support Are Effective for Serving Caregivers, Including Family, When Patients Are Approaching the End of Life?

Eight systematic reviews (25, 27, 29, 129–133) and 19 intervention trials (103, 104, 134–150) addressed caregiver outcomes (Table and Appendix Tables 1 and 3). An older review of 4 RCTs found that palliative care improved caregiver satisfaction (129). A meta-analysis found no overall benefit of palliative care teams (effect size, 0.16 [CI, –0.14 to 0.48]) in 13 mostly nonrandomized studies (25). A review of supportive cancer care (22 interventions, 5 randomized trials) identified 3 studies reporting improved caregiver satisfaction (27). A review of end-of-life care identified 5 randomized studies evaluating family or caregiver satisfaction with palliative care, with several reporting high satisfaction but only 1 demonstrating improvement (29).

A meta-analysis of caregiving for frail elderly patients with dementia found benefits in 11 intervention studies (effect size, 0.26 [CI, 0.15 to 0.37]) (130). Two partially overlapping and less complete reviews about dementia found no benefit for caregiver interventions (131, 132). A meta-analysis of 6 dementia outcomes (with 4 to 45 randomized, before-and-after studies and 1 to 11 randomized studies of long-term follow-up, depending on outcome) showed reduced symptoms in the care recipient in the short term, as well as reduced caregiver burden and depression, improved caregiver ability and knowledge, and longer follow-up studies (133). Two reviews found individual and multicomponent interventions more effective than group or single-component strategies (130, 133).

Nineteen additional studies (9 interventions, plus the several interventions and 6 sites in the REACH [Resources for Enhancing Alzheimer's Caregiver Health] project) assessed caregiver satisfaction or burden in end-of-life care (103, 104, 136–150). Five interventions focused on cancer, and 4 focused on palliative care or mixed populations. Interventions included case management, palliative care and advance care planning, care coordination, telephone support, and problem-solving interventions for cancer.

The SUPPORT (Study to Understand Prognoses and Preferences for Outcomes and Risks for Treatment) RCT provided improved information and communication for inpatients with poor prognoses, which improved caregiver satisfaction with communication (136, 137). In a study of

patients with cancer who were randomly assigned to comprehensive palliative care or telephone palliative care support, patient and caregiver satisfaction with care was high in both groups (135). A cluster-randomized trial of hospital-based palliative consultations for community oncology patients and providers was associated with improved after-death satisfaction for family members (138, 139). Randomized ICU ethics consultations were regarded favorably by 87% of patients, caregivers, physicians, and nurses (103, 104). Satisfaction was high and did not differ among groups in an RCT of a nursing home advance directive program ("Let Me Decide" booklet) (149).

The REACH project (available at www.edc.pitt.edu/reach/abstract.html) is a multisite project that uses common measures and procedures to test diverse interventions for dementia caregivers. Interventions included various skills training, emotional and behavioral assistance, in-home support, and enhanced technologies. The effect of the 9 interventions on caregiver burden (pooled result from the Revised Memory and Behavior Problems Checklist, a 0- to 96-point scale that summarizes 24 problem behaviors and accounts for the caregiver bother associated with each) was small but significant (-1.40 ; $P = 0.022$). With respect to depression, only 1 REACH site reported improvement in the Center for Epidemiologic Studies Depression Scale. The site used family therapy combined with a computer support system that facilitated connections to local resources and family conferencing (141, 142, 145–148).

In summary, weak to moderate evidence suggests that caregiver interventions, especially when comprehensive and individually targeted, can relieve burden, although effect sizes are generally small. Moderate evidence suggests that palliative care interventions improve satisfaction. Because existing research focuses on dementia, evidence is moderate in dementia and weak in cancer. No evidence addressed caregivers in heart failure. Addressing these deficits in caregiver research is critical because of the growing role of family caregivers for an increasing number of persons at the end of life.

DISCUSSION

We identified 33 systematic reviews and 89 reports of interventions from approximately 25 000 total citations relevant to improving the care of pain, dyspnea, and depression; advance care planning; care continuity; and caregiving. Most palliative and end-of-life care research addressed populations with cancer or advanced unspecified illness in which cancer is common. Other than the literature on cancer, much of this research focused on patients with advanced rather than terminal illness. Our evidence base for improving dyspnea and continuity of care and addressing caregiving burdens relies (to a large degree) on such indirect evidence. Most of the evidence base arises from studies of 1 setting of care, and few reports address nursing homes.

We found strong evidence for many pharmacologic treatments for cancer pain. Strong evidence supports β -agonists, morphine, pulmonary rehabilitation, and oxygen for symptomatic care of COPD, and opioid use is weakly supported for cancer dyspnea. Antidepressants have strong support for treating depression. Strong evidence supports the use of multidisciplinary interventions to enhance continuity and reduce inappropriate utilization. Weak to moderate evidence suggests that multifaceted, individually targeted caregiver programs can relieve burden.

We found weak evidence for the effectiveness of specific palliative service delivery innovations for managing pain and dyspnea, and we found no evidence that they improve depression. We found no evidence addressing pain management in advanced noncancer conditions, and insufficient evidence addressing dyspnea in cancer and heart failure. We identified research priorities about short-acting antidepressants and caregiving challenges in populations other than patients with dementia.

A recent systematic review found symptoms to be commonplace in late life across conditions (151). Because our review shows that treatment is effective, assessment and follow-up of pain, dyspnea, and depression are clinical priorities. Palliative care teams may be effective because they ensure symptom screening, treatment, and follow-up. Symptom research priorities include evaluation and management of pain in noncancer conditions, dyspnea in cancer, depression in late life (for example, short-acting antidepressants), and symptoms in the cognitively impaired.

Given the lack of patient- and family-centered measures (152), older research has focused on legal, administrative, and utilization outcomes of advance care planning. However, more recent research emphasizes broader interventions—including trained facilitators, involving key decision makers, and addressing care across settings. Recent literature has focused on special settings (for example, ICU or nursing home). Research should evaluate advance care planning in various conditions (for example, outpatients with advanced heart failure) and across settings.

Palliative care trials that have improved continuity did not compare various approaches. Heart failure research affirms the effectiveness of comprehensive interventions that ensure comprehensive support across time and settings. Such research has targeted utilization, with less attention to patient- and family-centered outcomes. Care coordination and continuity become especially difficult at the end of life when the patient faces complex transitions. For example, 25% of Oregonians use 3 or more settings during their last 4 weeks of life (128).

Most studies about caregiving focused on dementia, with some on cancer. Individual interventions yielded larger treatment effects, yet group interventions predominate in the literature. Multicomponent interventions show more consistent improvement in caregiver burden, although the effect size is generally small. Future research

should compare alternative strategies and include other common patient conditions.

Limitations of our review include that much of the literature relevant to these domains and the care of patients with advanced illness does not have a common keyword or indexing term. We dealt with this challenge by conducting disease-specific supplemental searches, but we may have missed relevant citations. Our study did not address certain domains (for example, spiritual support or bereavement) or technical interventions (for example, palliative surgery); future reviews will have to address these topics.

In summary, our systematic review identified interventions that could generate substantial improvement in the end-of-life experience. For example, the evidence base for improving cancer pain makes failing to relieve pain clearly unjustifiable (2). Although we address important research gaps, the rapid aging of our population makes implementation of current knowledge crucial in order to assure the highest possible quality of care throughout the lifespan.

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Disclaimer: The views expressed herein do not represent the views of the U.S. Department of Veterans Affairs, Agency for Healthcare Research and Quality (AHRQ), or National Institute of Nursing Research.

Grant Support: The National Institute of Nursing Research and the Agency for Healthcare Research and Quality (grant no. 290-02-0003) provided funding for this project. Dr. Lorenz was supported by a Veterans Affairs Health Services Research & Development Service Career Development Award, and Dr. Dy was supported by a K07 award from the National Cancer Institute (K07-CA096 783).

Potential Financial Conflicts of Interest: *Grants received:* K.A. Lorenz (Amgen).

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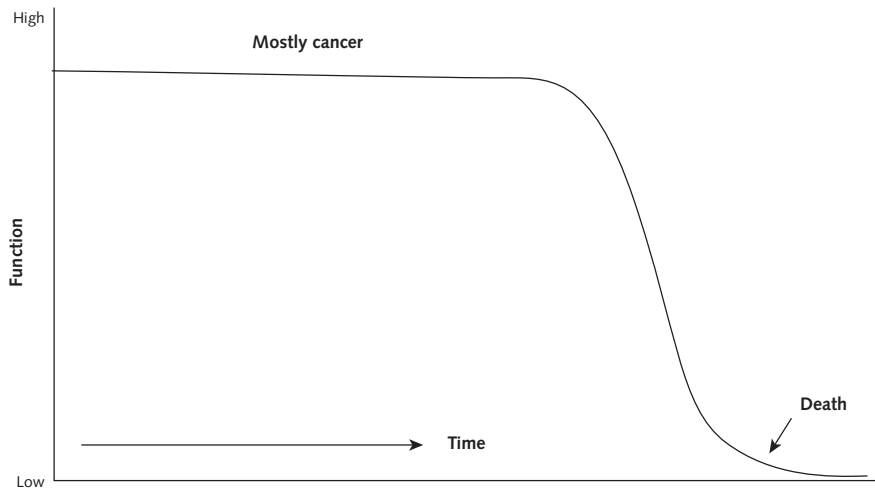
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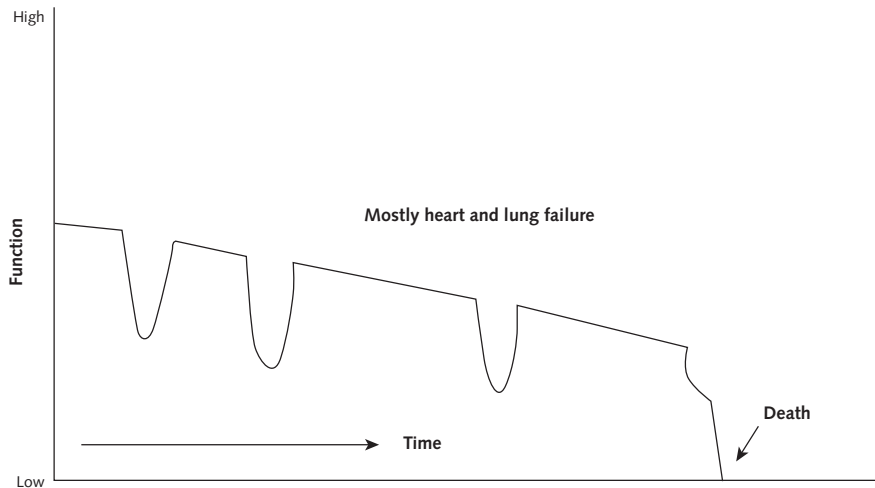
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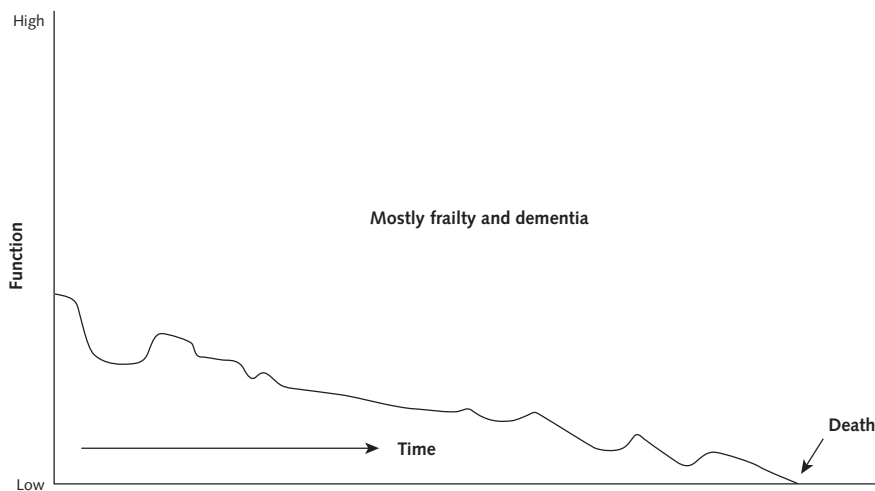
Appendix Figure. Trajectories of late-life illness.



Short Period of Evident Decline



Long-Term Limitations with Intermittent Serious Episodes



Prolonged Dwindling