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A Systematic Review of Health Care Interventions for Pain in Patients With Advanced Cancer

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Abstract

Purpose—Poorly controlled pain is common in advanced cancer. The objective of this article was to synthesize the evidence on the effectiveness of pain-focused interventions in this population.

Methods—We searched MEDLINE, CINAHL, PsycINFO, Cochrane, and DARE from 2000 through December 2011. We included prospective, controlled health care intervention studies in advanced cancer populations, focusing on pain.

Results—Nineteen studies met the inclusion criteria; most focused on nurse-led patient-centered interventions. In all, 9 (47%) of the 19 studies found a significant effect on pain. The most common intervention type was patient/caregiver education, in 17 (89%) of 19 studies, 7 of which demonstrated a significant decrease in pain.

Conclusions—We found moderate strength of evidence that pain in advanced cancer can be improved using health care interventions, particularly nurse-led patient-centered interventions.

Keywords

advanced cancer; pain; end of life; health care interventions; systematic review; quality improvement

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Corresponding Author: Kathryn A. Martinez, PhD, MPH, Division of General Medicine, University of Michigan, North Campus Research Complex, 2800 Plymouth Road, Building 16, 4th Floor, Ann Arbor, MI 48109, USA. makathry@med.umich.edu. **Declaration of Conflicting Interests**: The authors declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

Introduction

Pain is one of the most common symptoms in individuals with cancer and is directly associated with significantly reduced quality of life (QOL).^{1,2} Poorly managed cancer pain is an important quality-of-care outcome and a high priority for patients, clinicians, and health care policy makers.³ Despite the importance of pain assessment and management, undertreatment is common.^{4,5} In one institution, as many as 40% of the patients were found to be undertreated for pain.⁶ Because pain often changes with disease progression, frequent reassessment and changes in management are required to ensure optimal QOL and care.⁷ Although present throughout the disease progression, cancer-related pain may be more severe for terminally ill patients, particularly within the last days to weeks prior to death.⁸

Health care interventions may help to improve the management of pain in patients with advanced cancer, thereby reducing the quality gap—the difference between health care processes or outcomes observed in practice and what ideally could be achieved with proper application of evidence-based practices.⁹ Prior studies have found that barriers to pain management occur as a result of patient/caregiver, provider, and/or system barriers.¹⁰⁻¹² As a result, strategies to improve pain management in advanced disease may include methods such as patient and/or caregiver education, provider education, systematic pain assessment, and use of clinical decision support tools to promote appropriate prescribing of analgesia.

Previous systematic reviews have had mixed findings regarding the impact of interventions for pain in patients in various stages of cancer. A 2001 review of pain management interventions in general cancer populations found evidence for the effectiveness of nurse-led patient-centered educational interventions on pain but not for provider-focused interventions.¹³ More recent reviews in general cancer populations have supported these findings for patient-centered interventions^{14,15} but less evidence for institutional interventions for improved pain management.^{16,17}

These previous reviews addressed general cancer populations. Indeed, no previous review has specifically addressed advanced cancer populations primarily composed of patients with limited life expectancy. In advanced cancer populations, pain rapidly changes over time and is often due to complex etiologies and thus is often more severe. Such patients frequently have multiple coexisting symptoms and other sources of suffering; thus, the effects of interventions on pain outcomes may differ in this population. Consequently, we conducted a systematic review to evaluate the effectiveness of health care interventions targeting pain in patients with advanced cancer. We also assessed the impact of these interventions on patient pain knowledge and barriers as well as patient QOL. This review is part of a larger systematic review assessing the evidence for interventions to improve health care for patients with advanced and serious illness, broadly.¹⁸

Methods

We searched PubMed, CINAHL, PsycINFO, Cochrane, and DARE and identified additional studies from reference lists of eligible articles and relevant systematic reviews, as part of an overall review of interventions to improve health care for patients with advanced and serious

illness.¹⁸ Since the nature of both health care interventions and pain management has changed substantially since 2000, and other previous reviews have addressed the pre-2000 literature, we began our searches in 2000 and searched through December 2011. Search strategies for the overall review can be found in the e-appendix (online only).

We included prospective studies with control groups (both randomized and nonrandomized) that included a majority of patients with advanced cancer and/or who were unlikely to be cured, to recover, or to stabilize (palliative care population definition adapted from the National Consensus Project for Quality Palliative Care).¹⁹ Two independent reviewers evaluated each study to establish that the included study populations met this definition. We used a relatively broad definition of health care interventions, including studies conducted within or linked with the health care system and that have at least some element of system change. Because of the importance of patient-centered interventions for improving pain management, we included patient education and self-management interventions in this definition, as long as they were linked to the provision of health care. For the portion of the review described here, we included studies where the focus of the intervention was improving patients' pain and where pain was included as an outcome.

Two reviewers independently screened at the abstract and then at the full article level for eligibility (Figure 1). One reviewer abstracted data from included articles, which were checked by a second reviewer. We abstracted information on population characteristics, study design, setting, description of interventions, types of health care interventions used, study outcomes, including pain, QOL, patient knowledge of appropriate pain management practices, patient-reported barriers to pain management, and study statistics. We did not conduct meta-analysis because the reporting of outcomes was too heterogeneous to allow for quantitative synthesis.

We graded the strength of the evidence regarding the effectiveness of interventions in improving pain control, QOL, and patient barriers and knowledge, taking into consideration the risk of bias in relevant studies, using the Grading of Recommendations Assessment, Development, and Evaluation (GRADE) Working Group criteria adapted by the Agency for Healthcare Research and Quality Evidence-based Practice Centers Program (for details see reference 18).¹⁸

Results

Study Characteristics

We screened 13 014 titles and abstracts and 447 articles; 96 met the criteria for full review. Of these 96 articles, 19 met all the inclusion criteria for health care interventions targeting pain in patients with advanced cancer (Figure 1).

The 19 included studies spanned the years 2000 to 2011. The median sample size was 97 patients (range 43-185; Table 1). In all, 16 studies examined mixed cancer populations, while 1 study examined gynecologic cancers,²⁰ and 2 studies examined lung cancer only.^{21,22} Fifteen studies were conducted in an ambulatory setting, 3 were conducted in home care, ²³⁻²⁵ and 1 in a hospital.²⁶ Mean age of study participants, by study, ranged from

52 years to approximately 65 years, with a median of 59.5 years. Median follow-up time following the initiation of the health care intervention was 8 weeks (range 2-24 weeks), with the exception of 1 study, which performed follow-up to the patient's death.²⁷ In all, 14 (68%) of the 19 studies were conducted in the United States, 1 in Canada,²³ 1 in Australia,²⁶ 1 in Italy,²⁷ and 2 in the Netherlands.^{25,28}

Of the 19 studies, 16 (84%) were randomized-controlled trials (RCTs). All studies randomized at the patient level except for $1,^{29}$ which randomized by institution. Six studies were conducted in a single setting, and 13 were conducted in multiple settings, ranging from 2 to 21 sites. The 3 non-RCT studies used nonequivalent control groups (Table 1)^{85,88,93}.^{21,23,30} Patient pain was the target in all 19 (100%) of the studies (Table 2).

Risk-of-bias scores were high for 7 studies,^{20,26,29,31-34} medium for 7,^{21-23,27,30,35,36} and low for 5.^{24,25,28,37,38} Some RCTs did not fully report the randomization process, and many did not report blinding of outcome assessment.

Types of Health care Interventions

Table 1 describes the types of interventions used in the 19 included studies. Four (24%) studies used provider education as a component of the intervention.^{23,29-31} One study²² used a patient and caregiver reminder system as a component of their intervention. Seventeen (89%) studies employed patient and/or family education and promotion of self-management. Among those 17 studies that used patient and/or family education and promotion of self-management, 11 (58%) included multiple contacts with the patient.^{20-22,24,25,28,29,30-33,35-37} Number of follow-up contacts among these studies ranged from 1 brief 10-minute follow-up³³ or phone call³⁶ to 10 individual contacts over the course of 20 weeks.³¹

The majority (89%) of the studies examined patient-centered educational interventions. Two studies focused on provider-level interventions only; one of these studies²⁷ was an intervention evaluating the use of strong opioids as first-line therapy in cancer pain management, and the other²⁹ employed a provider education program about using an algorithm to improve cancer pain management.

Outcomes

Barriers and Knowledge

Knowledge and/or barriers to pain management were assessed in 12 (71%) of the 17 studies. Most of these studies used the Barriers Questionnaire (BQ).^{20,21,26,30,33–34} One study used a modified version of the BQ, which included only 2 subscales (communication and analgesic use).³² Studies that did not use the BQ used the Family Pain Questionnaire,²³ the Patient Barriers Survey,²⁹ Ferrell's Pain Questionnaire,^{25,28} or a 6-item scale adapted from the American Pain Society Guidelines for the Treatment of Pain Patient Outcome Questionnaire.³⁴ In addition to the BQ, 2 studies also used the Patient Pain Knowledge Tool.^{21,30}

In all, 6 (55%) of the 11 studies measuring barriers to pain management found statistically significant improvements as a result of the interventions^{21,23,26,30,33–34}; however, one of

Of the 5 studies that specifically measured pain knowledge^{21,25,28,30,34} 2 showed a significant improvement in pain knowledge.^{28,29} One of these studies also found a significant impact of the intervention on patient pain.²⁸

Pain

Table 2 describes outcomes assessed by each study. All 19 studies assessed pain as an outcome. In all, 14 (74%) of the 19 studies used the Brief Pain Inventory (BPI) as the pain measurement tool. In studies using the BPI, components included worst pain, average pain, usual pain, current pain, least pain, pain relief, and pain interference. This is further described in Table 2. One study²¹ used the Quality of Life Scale/Cancer Patient Tool, one³¹ used the Symptom Experience Scale, one²⁷ used a visual analog scale, and one used the McGill Pain Questionnaire.²² One other study used a demographic and treatment data collection tool to determine patient pain experience.³⁰

Because of the heterogeneity of outcome and statistics reporting, results are summarized by whether or not there was a statistically significant improvement in outcomes in the intervention compared to the control group. In all, 9 (47%) of the 19 studies showed statistically significant improvement with the health care intervention on pain scores compared to the control group; 4 studies found significant effects for usual/average pain,^{23,29,33,34} 2 studies demonstrated significant improvements in both average and worst pain scores,^{26,37} 2 studies^{27,37 89 96} showed significant differences by group on scores for current pain, and 1 study found significant effects for average pain and current pain.²⁸ One study, which used a visual analog scale to measure pain rather than the BPI, also found significant pain improvements.²⁷ The strength of evidence for the outcome of pain was moderate.

Four studies that used an educational video followed by printed materials to enhance the educational intervention showed statistically significant improvement in pain scores;^{23,25,33,37} and while 2 other studies that used either print material alone²⁰ or video material alone²² showed no positive effect of the intervention, 1 study using print material alone following the educational intervention showed a significant positive impact on patient pain.²⁸ Two additional studies using a combination of print and video material^{28,32} did not demonstrate a positive effect on the intervention of pain. This suggests moderate evidence that combining multiple educational modalities may have a positive effect on reducing patient pain.

Among interventions with significant improvements in pain scores, the number of patient encounters ranged from $1^{23,26,34}$ to $8,^{28}$ with a mean number of encounters of 3. Among interventions without significant improvements in pain score, the number of patient encounters ranged from 1^{36} to $10,^{31}$ with a mean number of contacts of 4. Of the 7 effective

interventions that targeted patients and caregivers, 4 were conducted in ambulatory settings, 2 in home care settings,^{23,24} and 1 in a hospital settings.²⁶

Quality of Life

In all, 9 (47%) of the 19 studies measured QOL; however, only 1^{37} found a statistically significant improvement in QOL. Moreover, this 1 study only found improvement in a single subscale of a QOL measure, the SF-36 subscale for body pain. Of the 9 studies that measured QOL, both cancer-specific QOL instruments and general QOL instruments were used to asses patient QOL. Cancer-specific instruments included the Functional Assessment of Cancer Therapy–General (FACT-G)²⁰ and the Quality of Life Index–Cancer Version (QLI-CV).³⁴ Noncancer-specific instruments used to assess QOL in these studies included the SF-12^{35–36} SF-36,³⁷ both from the Medical Outcomes Study (MOS) and from the Uniscale for Global QOL²⁶ and the Multidimensional Questionnaire.²⁷ Strength of evidence was low.

Discussion

Our review found moderate strength of evidence that health care interventions improved pain in patients with advanced cancer. Almost all of the included studies employed patient and caregiver education as the predominant intervention, with half of these studies showing no statistically significant reductions in pain scores. Although only 2 of the 19 studies focused specifically on provider behavior,^{27,29} they both found statistically significant improvements in patient pain levels.

Pain knowledge and beliefs can have an impact on appropriate pain control for patients with cancer. In particular, fears of addiction to opioid analgesia are frequently reported as a barrier to cancer pain management.⁶ The majority of the studies included in this review measured patient knowledge or barriers, although only half found a positive effect of the intervention on patient-reported barriers scores. Moreover, only 4 (33%) of 12 studies that measured both patient pain and patient knowledge and/or barriers reported positive intervention effects on both the factors. This may be due to the timing of the intervention relative to the measurement of the outcomes. It is possible that despite immediate changes in knowledge and barriers, concomitant reductions of pain may lag somewhat behind. This could be the result of either innate features of the patient's disease progression or not having been seen by a provider for reassessment and medication changes since the intervention.

No studies found an impact on overall QOL. Instruments used to measure QOL in the included articles were not specifically developed or validated in advanced cancer populations, which may have limited their utility in detecting changes in QOL in this population. Although pain levels and QOL have been found to be associated among patients with cancer,¹ none of these studies explored the relationship between pain and QOL directly.

Although a prior review of pain interventions in general cancer populations suggested a dose–response relationship of patient education and pain outcomes,¹⁵ we did not observe this pattern in our review. Of the 7 effective studies using patient education as the main health care intervention strategy, 3 relied on a single contact with patients and 2 more

studies included a single contact with a 1-time 10-minute follow-up. It is possible that we were unable to observe such a dose–response relationship in our review because of the restriction of our sample to include only patients with advanced cancer as opposed to a more general cancer population. Higher intensity of services may not be as strongly correlated with outcomes in this population due to the difficulties of conducting longitudinal studies in patients with advanced cancer.

The limitations of the identified literature and this review are as follows. This review was restricted to studies predominantly of patients with advanced cancer, and thus many institutional-level studies that addressed more general populations were not included. In addition, many of the included studies had small sample sizes. While hospice is an important source of care for patients with advanced cancer and pain treatment, we identified no studies focused specifically on pain management in hospice care. An inherent limitation of studying individuals with advanced cancer is a high rate of attrition due to either death or an inability to complete the study due to advancing illness. An additional limitation of this review is that it only included studies focused on pain, and thus the generalizability of these findings is limited to health care efforts focused on pain as a single symptom.

Racial and ethnic disparities in cancer pain are widely reported in the literature and represent a clear priority area for quality improvement in cancer care.^{5,39} However, studies included in this review did not include a sufficient number of minority patients to do subgroup analyses or minority status was not reported. Thus, we were unable to determine possible differential effectiveness of these pain-focused health care interventions by racial or ethnic group. Given persistent disparities in pain, this is an important area for future research.

Due to the heterogeneity of the literature in this review, we were unable to perform a metaanalysis. Although most studies used the BPI to assess pain, they used different components of the BPI, which complicated comparisons across studies. This variability in the measurement and reporting of the BPI (as shown in Table 2) is a major limitation in this area of research, and efforts to evaluate health care interventions targeting pain in this high-need population would benefit from standardization of pain measurement and outcome reporting.

Health care interventions aimed at reducing the burden of pain in this population are important, but heterogeneity both in interventions and in outcome measurement pose challenges to determining optimal types of interventions for pain management. Findings from this review suggest that provider-focused interventions to standardize patient pain management practices demonstrate promising outcomes; however, more research is needed.

Undertreatment of pain in advanced cancer populations represents a major quality problem in cancer care. Given the association between high levels of pain and poor QOL, reducing the burden of pain experience in individuals with advanced disease should remain a priority. Improving pain management in patients with advanced cancer, however, is a complicated, multistep process that includes pain screening by a provider, pain assessment, appropriate treatment, and continued patient monitoring to address changes in pain levels over time. These processes are further complicated by the need to address common coexisting symptoms that may affect pain management such as depression. Although evidence suggests

the benefit of nurseled, patient-centered educational interventions, further study is warranted to determine the appropriate intervention content, timing, and intensity. That said, there is evidence supporting the use of multiple simultaneous educational modalities in patientcentered interventions to optimize pain outcomes. Provider-focused interventions, aimed at standardizing pain management protocols in advanced cancer populations, also demonstrate

evidence of being effective in reducing patient pain burden. It is possible that a combination of provider- and patient-focused interventions for pain management would yield the greatest reductions in patient pain burden. This is an important topic for future research to ameliorate unnecessary suffering among patients with advanced cancer.

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Table 1

Study Characteristics of Included Articles.

Author/Year	Study Design	Sample Size ^a	Setting	Intervention
Anderson, 2004	RCT	97	Ambulatory	Patient education consisting of race- and gender-tailored video, followed by a nurse-led meeting and a follow-up call
Aubin, 2006	Non-RCT	80	Home care	1-time nurse-led patient-focused educational intervention including a pain diary, video, and pain monitoring recommendations
Borneman, 2008	Non-RCT	46	Ambulatory	4-part patient-focused educational intervention pertaining to pain assessment, pain management, and fatigue
Borneman, 2010	Non-RCT	157	Ambulatory	4-part patient-focused educational intervention pertaining to pain assessment, pain management, and fatigue
Dalton, 2004	RCT	127	Ambulatory	Nurse-led profile-tailored patient-focused cognitive behavioral treatment program
Du Pen, 2000	RCT	105	Ambulatory	Provider-focused education intervention on implementing a previously tested algorithm for cancer pain management
Given, 2002	RCT	113	Ambulatory	10-part nurse-implemented patient-focused pain and fatigue management educational intervention
Keefe, 2005	RCT	78	Home care	3-session nurse-led patient-focused partner-guided pain management intervention
Lovell, 2010	RCT	185	Hospital	Patient-focused pain management educational intervention utilizing a booklet and a video
Marinangeli, 2004	RCT	92	Ambulatory	Use of strong opioids as first line therapy in cancer pain management
Miaskowski, 2004 and Miaskowski, 2007 ^a	RCT	174; 167	Ambulatory	6-week patient-directed nurse-led psychoeducational intervention
Oldenmenger, 2011	RCT	72	Ambulatory	Patient-directed pain consult plus specialized nurse-conducted patient education program (PEP).
Oliver, 2001 Kalauokalani, 2007 ^a	RCT	67	Ambulatory	1-time individualized patient education and coaching session, administered by a trained health educator
Syrjala, 2008	RCT	78	Ambulatory	Nurse-led patient-focused training in cancer pain management using integrated print and video materials
van der Peet, 2004	RCT	120	Home care	3-visit patient-focused nurse-led pain education program
Ward, 2000	RCT	43	Ambulatory	Nurse-led patient-centered individually tailored information
Ward, 2008	RCT	176	Ambulatory	Single 1-on-1 patient-focused psychoeducational session based on the representational approach to patient education administered by a research nurse
Wells, 2003	RCT	64	Ambulatory	Patient-focused pain education with a hotline and pain education with provider-initiated follow-up telephone calls
Wilkie, 2010	RCT	151	Ambulatory	Individualized patient pain coaching on self-monitoring and reporting administered by trained research assistants

Abbreviations: RCT, randomized controlled trial; CBT, cognitive behavioral therapy.

 a Two articles found in the review that are about the same study, data abstracted as one study.

Table 2

Outcomes for Included Studies.

Author/year	Pain	QOL	BPI	BPI Measure Reported
Anderson, 2004	NS	NS	Y	Worst pain, pain interference
Aubin, 2006	S		Y	Average pain, worst pain
Borneman, 2008	NS			
Borneman, 2010	NS			
Dalton, 2004	NS	NS	Y	Worst, least, average, pain now, pain right now, pain interference with walking, sleep, relationships, activity, composite severity score, composite interference score
Du Pen, 2000	S		Y	Aggregate score of worst pain and usual pain
Given, 2002	NS			
Keefe, 2005	NS	NS	Y	Worst pain, usual pain
Lovell, 2010	S	NS	Y	Average pain, worst pain, pain interference
Marinangeli, 2004	S	NS		
Miaskowski, 2004 and Miaskowski, 2007 ^a	S	NS (except for 1 subscale)	Y	Least pain, average pain, worst pain Total interference score, individual scores for activity, mood, walking, work, relations with others, sleep, enjoyment of life, sexual activity
Oldenmenger, 2011	S		Y	Current pain, average pain, worst pain in past 24 hours; pain interference
Oliver, 2001 and Kalauokalani, 2007 ^a	S		Y	Average pain
Syrjala, 2008	S		Y	Usual pain, worst pain, interference with function (overall)
van der Peet, 2004	S	NS	Y	Present pain
Ward, 2000	NS	NS	Y	Worst pain, pain interference composite score
Ward, 2008	NS	NS	Y	BPI severity composite score, pain interference composite score
Wells, 2003	NS		Y	Worst pain, average pain, pain interference, pain relief
Wilkie, 2010	NS			

Abbreviations: S, significant; NS, not significant; BPI, brief pain inventory; QOL, quality of life; Y, Yes, used BPI.

 $^{a}\mathrm{Two}$ articles found in the review that are about the same study, data abstracted as one study.