

**Original Article**

# The Association of Depression and Pain with Health-Related Quality of Life, Disability, and Health Care Use in Cancer Patients

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**Abstract**

**Context.** Pain and depression are two of the most prevalent and treatable cancer-related symptoms, each present in at least 20%–30% of oncology patients.

**Objective.** To determine the associations of pain and depression with health-related quality of life (HRQL), disability, and health care use in cancer patients.

**Methods.** The Indiana Cancer Pain and Depression study is a randomized clinical trial comparing telecare management vs. usual care for patients with cancer-related pain and/or clinically significant depression. In this article, baseline data on patients enrolled from 16 urban or rural community-based oncology practices are analyzed to test the associations of pain and depression with HRQL, disability, and health care use.

**Results.** Of the 405 participants, 32% had depression only, 24% pain only, and 44% both depression and pain. The average Hopkins Symptom Checklist 20-item depression score in the 309 depressed participants was 1.64 (on 0–4 scale), and the average Brief Pain Inventory (BPI) severity score in the 274 participants with pain was 5.2 (on 0–10 scale), representing at least moderate levels of symptom severity. Symptom-specific disability was high, with participants reporting an average of 16.8 of the past 28 days (i.e., 60% of their days in the past four weeks) in which they were either confined to bed (5.6 days) or had to reduce their usual activities by 50% (11.2 days) because of pain or depression. Moreover, 176 (43%) participants reported being unable to work because of health-related reasons. Depression and pain had both individual and additive adverse associations with quality of life. Most patients were currently not receiving care from a mental health or pain specialist.

**Conclusion.** Depression and pain are prevalent and disabling across a wide range of types and phases of cancer, commonly co-occur, and have additive

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### **Key Words**

*Cancer, pain, depression, disability, quality of life, health care use*

## **Introduction**

Pain and depression are two of the most common and potentially treatable symptoms in cancer patients. Pain is present in 14%–100% of cancer patients, depending on the setting, and the prevalence of major depressive disorder is 10%–25%, with a similar range for clinically depressive symptoms.<sup>1–4</sup> These symptoms have a substantial adverse effect on functional status and quality of life<sup>5–9</sup> and are poor prognostic factors for survival in advanced cancer,<sup>10,11</sup> including a desire for hastened death.<sup>12</sup> Moreover, both depression and pain are frequently underdiagnosed in cancer patients,<sup>13–16</sup> and up to half of cancer patients depressed at baseline remain depressed at one-year follow-up.<sup>1</sup> Likewise, cancer pain often is undertreated.<sup>1,17,18</sup>

Although there is considerable research on the prevalence and impact of pain and depression as individual symptoms in cancer patients, as well as their frequent co-occurrence, there have been fewer studies on the independent and additive effects of pain and depression on health-related quality of life (HRQL) in the same patient population. Moreover, these studies have been limited by highly selected cancer patients, small sample size, and focus on a single HRQL outcome. For example, three studies focused on a desire for hastened death in terminally ill cancer patients; this outcome was associated with both depression and pain in one study<sup>12</sup> but only depression in the other two studies.<sup>19,20</sup> Three studies examined the individual associations of pain and depression with HRQL but did not examine their relative and combined effect.<sup>21–23</sup> A study of 115 cancer survivors found differential effects of pain, depression, and other symptoms on various domains of HRQL.<sup>24</sup>

The Indiana Cancer Pain and Depression (INCPAD) study is a clinical trial enrolling patients from community-based oncology practices who suffer from depression and/or

cancer-related pain and randomizing them to telecare management or usual care. INCPAD is, therefore, a good study in which to study the individual and combined effects of pain and depression. Our primary hypothesis for this article is that pain and depression in patients with cancer have independent and synergistic associations with both increased disability and poorer HRQL in domains not directly related to pain and mental health. Secondarily, we hypothesize that pain and depression are associated with increased health care use.

## **Methods**

### *Screening and Eligibility Interview*

Details of the INCPAD study methods have been previously reported.<sup>25</sup> Briefly, patients presenting for outpatient visits at one of the 16 urban and rural participating oncology practices in the state of Indiana between March 2006 and August 2008 were invited to complete a four-item depression and pain screener, consisting of the Patient Health Questionnaire two-item (PHQ-2) depression scale and the Short Form-36 (SF-36) Bodily Pain scale, both of which are well-validated measures for assessing depression and pain severity.<sup>26,27</sup> Patients who screened positive for pain (at least moderate pain severity or pain interference)<sup>27,28</sup> or depression (PHQ-2 score  $\geq 2$ )<sup>26</sup> and were potentially interested in the study underwent an eligibility interview.

*Depression.* Depression had to be of at least moderate severity, defined as a PHQ nine-item (PHQ-9) depression score of 10 or greater with either depressed mood and/or anhedonia being endorsed.<sup>29–31</sup> In previous studies, >90% of patients fulfilling this PHQ-9 criterion had major depression and/or dysthymia, and the remaining patients had clinically

significant depression with substantial functional impairment.<sup>29,32</sup>

*Pain.* Pain had to be 1) at least moderate in severity, defined as a Brief Pain Inventory (BPI) "worst pain in the past week" score of 6 or greater;<sup>17,33–35</sup> 2) persistent despite the use of one or more analgesics; and 3) cancer-related. Cancer-related is defined as pain occurring in the region of the primary tumor or cancer metastases and/or occurring after the onset of cancer treatment. Excluded were pre-existing pain conditions unrelated to cancer (e.g., migraine or tension headache, arthritis, back disorders, bursitis or tendonitis, injuries, and fibromyalgia).

Excluded were individuals who 1) did not speak English, 2) had moderately severe cognitive impairment as defined by a validated six-item cognitive screener,<sup>36</sup> 3) had schizophrenia or other psychosis, 4) had a disability claim currently being adjudicated for pain, 5) had depression directly precipitated by a cancer therapy for which depression is a well-known side effect (e.g., interferon and corticosteroids) and in whom short treatment duration and tolerable depression severity justify withholding antidepressant therapy, 6) were pregnant, or 7) were in hospice care.

### Study Measures

Depression diagnoses were established with the PHQ-9, which, with several added questions, categorizes individuals into three *Diagnostic and Statistical Manual of Mental Disorders* (Fourth Edition) diagnostic subgroups: major depression, dysthymia, and other depression.<sup>29</sup> Depression severity was assessed with the Hopkins Symptom Checklist 20-item (HSCL-20) depression scale,<sup>32,37,38</sup> which had an excellent internal reliability (Cronbach's  $\alpha = 0.89$ ) in our sample. Pain was assessed primarily with the BPI, which rates the severity of pain on four items (current, worst, least, and average pain in past week) and the interference in seven areas (mood, physical activity, work, social activity, relations with others, sleep, and enjoyment of life).<sup>17,39,40</sup> Internal reliability also was excellent for the BPI severity ( $\alpha = 0.79$ ) and BPI interference ( $\alpha = 0.89$ ) scales. The SF-36 Bodily Pain scale<sup>41</sup> ( $\alpha = 0.73$ ) provided a secondary measure of pain.

HRQL was assessed with the SF-12 physical component summary (PCS) and mental component summary (MCS) scores<sup>42</sup> ( $\alpha = 0.84$  for both), as well as the SF-36<sup>43,44</sup> Mental Health scale ( $\alpha = 0.82$ ), Vitality scale ( $\alpha = 0.75$ ), and a single general health perceptions item that has shown to predict long-term health outcomes.<sup>45</sup> Functional status, an important aspect of HRQL, was further assessed with the three-item Sheehan Disability Scale ( $\alpha = 0.82$ ) and a single-item overall quality-of-life measure.<sup>46,47</sup> In addition, disability days were assessed as the number of days during the preceding four weeks in which the patient was either in bed or had to reduce his/her work or usual activities by 50% or more.<sup>48,49</sup> This total number of disability days could, therefore, range from 0 to 28. Anxiety severity was assessed by the seven-item Generalized Anxiety Disorder (GAD-7) scale<sup>50,51</sup> ( $\alpha = 0.86$ ) for which the score ranges from 0 to 21 and which has proven to be a good screener for the most common anxiety disorders seen in medical patients.

Medication use (antidepressants, other psychotropics, and opioid and nonopioid analgesics) was extracted from each patient's oncology practice records. Also, patients were asked in the baseline interview about treatments they had received and practitioners they had seen for depression and/or pain. Self-reported health care use in the preceding three months of five types of health services was assessed: hospital days and visits to an outpatient physician, emergency department (ED), mental health professional, or complementary and alternative medicine (CAM) provider. Finally, in addition to gathering demographic information, medical comorbidity was assessed with a checklist of eight common medical disorders that have been shown to predict hospitalization and mortality.<sup>52</sup>

### Statistical Analysis

Characteristics of the three patient groups (pain only, depression only, and pain and depression) were described, and bivariate comparisons were tested using analysis of variance for continuous variables and Chi-square analysis for categorical variables. Because these bivariate comparisons were not adjusted for multiple comparisons, any differences among groups that are not highly significant ( $P < 0.001$ ) should be interpreted

cautiously. Depression- and pain-specific treatments also were described for the three groups without statistical comparisons.

Our primary outcomes of interest were three HRQL domains (vitality, general health perceptions, and overall quality of life) and two measures of disability (Sheehan Disability score and number of disability days). The relationships of the three HRQL outcomes and the Sheehan Disability score to pain and depression were examined in multivariable linear regression models. The relationship of total number of disability days in the preceding four weeks to pain and depression was examined in a multivariable log-linear regression model based on Poisson distribution. The dependent variable in each model was one of the HRQL or disability outcomes. The independent variables were HSCL-20 depression and BPI pain severity scores. The covariates were age, sex, race (white and other), medical comorbidity, educational level (less than high school vs. high school education or higher), income (not enough to make ends meet vs. comfortable or just enough to make ends meet), and employment status (unemployed or unable to work for health or disability reasons vs. employed, retired, homemaker, or student).

Multivariable models were run in four steps: pain only (Step 1), depression only (Step 2), pain and depression (Step 3), and pain and depression adjusting for covariates (Step 4). Steps 1 and 2 were run to explore the individual association of pain and depression with the outcomes. Step 3 aimed to determine the independent effects of pain and depression controlling for the presence of each other. Step 4 examined the independent effects of pain and depression while controlling for the effects of potential confounders. Results in the fully adjusted model (Step 4) were adjusted for multiple comparisons using a modified Bonferroni procedure.<sup>53</sup>

Secondarily, we explored differences among the three symptom groups in the five patient-reported measures of health care use. Because health care use was reported in ordinal categories, group differences were compared by Chi-square analysis and adjusted for multiple comparisons using a modified Bonferroni technique.<sup>53</sup> All analyses were performed using SAS Version 9.1 (SAS Institute, Cary, NC).

## Results

### Screening, Eligibility, and Enrollment

Fig. 1 summarizes the participant flow in terms of screening, eligibility, and enrollment. Of 4465 screening questionnaires received from the oncology clinics, nearly half ( $n=2185$ ; 48.9%) were positive for pain and/or depression. This represented 1851 unique patients who screened positive for depression and/or pain because 334 patients had screened positive on more than one occasion. We were able to contact and complete eligibility interviews in 1261 screen-positive patients. We enrolled 274 (61.7%) of the 444 patients who met all entry criteria for pain and 309 (67.2%) of the 460 patients who met entry criteria for depression. Our total enrolled sample was 405 patients, of whom 96 (23.7%) had pain only, 131 (32.3%) had depression only, and 178 (44.0%) had both pain and depression.

### Secondary Findings From Eligibility Interview

Additional questions were asked of the 578 patients whose pain was possibly cancer-related to better characterize pain location, duration, and severity. The location of pain was the back in 184 (31.8%), abdomen in 94 (16.3%), shoulders in 75 (13.0%), hip in 63 (10.9%), knees in 57 (9.9%), chest in 80 (13.8%), feet in 51 (8.8%), headache in 47 (8.1%), neck in 41 (7.1%), elbows or hands in 36 (6.2%), and generalized or widespread in 23 (4.0%). Pain was present in a single site in 37.7% of patients, two sites in 36.2%, and three or more sites in 26.1%. Pain had been present for less than a month in 13%, one to three months in 24%, four to 12 months in 27%, one to five years in 29%, and more than five years in 7%. The proportion of patients rating their average pain in the past week on a 0–10 scale as 1–3 (mild), 4–6 (moderate), and 7–10 (severe) was 37.4%, 55.5%, and 7.1%, respectively. However, the proportion rating their worst pain as 6 or greater (a study entry criterion) was 444 (76.8%) of the 578 patients.

Of the 1261 patients who screened positive for depression and/or pain and who completed an eligibility interview, the distribution of PHQ-9 depression scores was 0–4 (no to minimal depressive symptoms), 5–9 (mild),

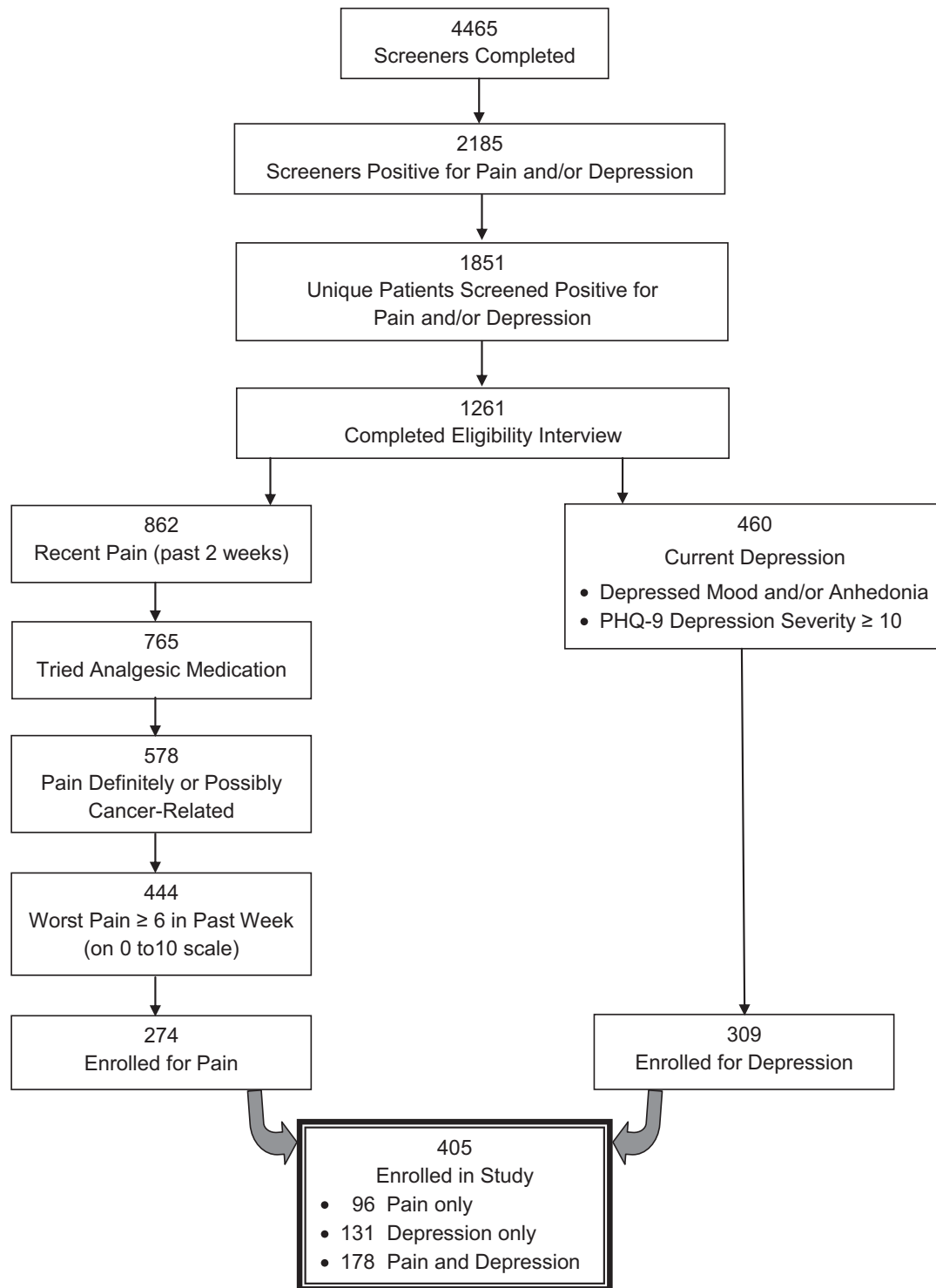


Fig. 1. Flow diagram of screening and enrollment of participants in INCPAD study.

10–14 (moderate), and  $\geq 15$  (moderately severe to severe) in 42.7%, 20.9%, 19.5%, and 16.0%, respectively. A total of 460

(36.5%) patients met the entry criteria for depression (PHQ-9 score  $\geq 10$  and either depressed mood or anhedonia).

### *Characteristics of the Overall Sample*

Table 1 compares characteristics of the study participants across the three study groups. Overall, the 405 study participants had a mean age of 58.8 years, 68% were women, and 20% were minority (principally African American). The type of cancer was breast in 118 (29%) of the participants, lung in 81 (20%), gastrointestinal in 70 (17%), lymphoma or hematological in 53 (13%), genitourinary in 41 (10%), and other in 42 (10%). The phase of cancer was newly diagnosed in 150 (37%) of the participants, disease free or maintenance therapy in 172 (42%), and recurrent or progressive in 83 (21%). Medication information obtained from the oncology practice records indicated that antidepressants (excluding tricyclics) were taken by 150 (37.8%) of the study participants at baseline and opioid analgesics by 214 (54.0%).

The 405 study participants reported an average of 16.8 of the past 28 days (i.e., 60% of their days in the past four weeks) in which they were either confined to bed (5.6 days) or had to reduce their usual activities by 50% (11.2 days) because of pain or depression. Moreover, 176 (43%) reported being unable to work because of health-related reasons. The mean SF-12 PCS score of 32.7 substantiates the rather severe degree of impairment, as does the mean SF-36 Vitality (28.3) and General Health Perceptions (28.2) scores.

### *Symptom Severity and HRQL*

The average SCL-20 depression score in the 309 depressed participants was 1.64 (on a 0–4 scale), and the average BPI severity score in the 274 participants with pain was 5.2 (on a 0–10 scale), representing at least moderate levels of symptom severity. As expected, the pain-specific (BPI severity and SF bodily pain) scores were higher in the pain only and depression and pain groups, whereas the depression and mental health-specific (SCL-20, GAD anxiety, and SF MCS) scores were higher in the depression only and depression and pain groups (Table 1). In terms of the three more generic HRQL measures (general health perceptions, vitality scores, and overall quality of life), the depression-only group tended to have worse scores than the

pain-only group, with the worst scores seen in the group with comorbid pain and depression.

### *Disability*

There was an incremental increase in total disability days in the past four weeks as one went from the pain only (12.2 days) to depression only (16.5 days) to comorbid pain and depression (19.6 days) subgroups. Likewise, the proportion of patients being unable to work because of health-related reasons progressively increased among these three groups (28% vs. 39% vs. 55%), as did the Sheehan Disability Index (3.7 vs. 5.5 vs. 6.4).

### *Self-Reported Treatments for Pain and Depression*

Table 2 summarizes the treatments that patients reported taking for their pain and depression. Only a minority of patients reported receiving current care from a mental health professional or taking St. John's Wort or other herbal treatments. Most patients were taking a medication for their pain, whereas few reported nonpharmacological treatments. Of the 258 subjects enrolled in the study for pain who provided information on hours of relief from their pain medication, more than one-third ( $n = 95$ ; 36.8%) reported three hours or less of relief. Patients in the pain-only group reported that pain medications relieved 69.8% of their pain, whereas patients in the pain and depression group reported 63.4% relief. Although many patients with pain reported seeing a variety of specialists sometime in their lifetime for pain, few were currently going to a pain clinic (6.9% of those enrolled for pain) or receiving physical therapy, chiropractic care, massage therapy, or acupuncture. Consulting other specialists for pain was only asked in terms of lifetime use, and here, the most commonly seen were orthopedics and neurology.

### *Association of Depression and Pain with HRQL and Disability*

As noted previously, multivariable regression models were run in four steps for the each of the three generic HRQL outcomes and two disability measures. Table 3 shows the results of these four models for each dependent variable. In the final models, which included both pain and depression as well as covariates and were adjusted for multiple comparisons, depression

Table 1  
Baseline Characteristics of 405 Subjects by Pain and Depression Group

Baseline Characteristics	Pain Only (n = 96)	Depression Only (n = 131)	Depression and Pain (n = 178)	P-value
Mean (SD) age, year	60.3 (9.7)	60.3 (11.0)	57.0 (11.0)	0.009
Women, n (%)	66 (68.8)	94 (71.8)	115 (64.6)	0.40
Race, n (%)				0.20
White	72 (75.0)	110 (84.0)	140 (78.7)	
Black	22 (22.9)	16 (12.2)	35 (19.7)	
Other	2 (2.1)	5 (3.8)	3 (1.7)	
Education, n (%)				0.34
Less than high school	23 (24.0)	24 (18.3)	40 (22.5)	
High school	31 (32.3)	63 (48.1)	66 (37.1)	
Some college or trade school	29 (30.2)	31 (23.7)	48 (27.0)	
College graduate	13 (13.5)	13 (9.9)	24 (13.5)	
Married, n (%)	48 (50.0)	67 (51.2)	77 (43.3)	0.24
Employment status, n (%)				<0.0001
Employed	33 (34.4)	22 (16.8)	26 (14.6)	
Unable to work because of health or disability	27 (28.1)	51 (38.9)	98 (55.1)	
Retired	30 (31.3)	48 (36.6)	39 (21.9)	
Other	6 (6.3)	10 (7.6)	15 (8.4)	
Income level, n (%)				0.018
Comfortable	31 (32.3)	32 (24.4)	37 (20.8)	
Just enough to make ends meet	50 (52.1)	60 (45.8)	82 (46.1)	
Not enough to make ends meet	14 (12.6)	38 (29.0)	59 (33.2)	
Mean (SD) no. of medical diseases	1.84 (1.50)	2.05 (1.44)	2.22 (1.76)	0.18
Type of cancer, n (%)				0.37
Breast	24 (25.0)	48 (36.6)	46 (25.8)	
Lung	18 (18.8)	28 (21.4)	35 (19.7)	
Gastrointestinal	16 (16.7)	19 (14.5)	35 (19.7)	
Lymphoma and hematological	16 (16.7)	13 (9.9)	24 (13.5)	
Genitourinary	12 (12.5)	14 (10.7)	15 (8.4)	
Other	10 (10.4)	9 (6.9)	23 (12.9)	
Phase of cancer, n (%)				0.32
Newly diagnosed	31 (32.3)	46 (35.1)	73 (41.1)	
Maintenance or disease-free	40 (41.7)	62 (47.3)	70 (39.3)	
Recurrent or progressive	25 (26.0)	23 (17.6)	35 (19.7)	
Major depression, n (%)	0 (0.0)	71 (54.2)	119 (66.9)	<0.0001
Baseline medication use, n (%) <sup>a</sup>				
Antidepressants (excluding tricyclics)	24 (25.3)	56 (44.4)	70 (40.0)	0.01
Tricyclic antidepressants	4 (4.2)	13 (10.3)	18 (10.3)	0.19
Psychotropics (excluding antidepressants)	26 (27.4)	38 (30.2)	51 (29.1)	0.90
Opioid analgesics	51 (53.7)	55 (43.7)	108 (61.7)	0.008
Nonopioid analgesics	43 (45.3)	61 (48.4)	74 (42.3)	0.57
Mean (SD) scale scores				
BPI pain severity (score range 0–10)	4.85 (2.03)	2.28 (2.10)	5.41 (1.67)	<0.0001
SCL-20 depression (score range 0–4)	0.82 (.56)	1.51 (.58)	1.73 (.66)	<0.0001
Mean SF functional status (score range 0–100)				
General health perceptions	36.2 (29.0)	32.4 (30.6)	20.8 (24.8)	<0.0001
Vitality	41.5 (20.5)	26.5 (17.9)	22.4 (15.8)	<0.0001
Mental Health	74.3 (17.2)	50.5 (18.6)	49.9 (20.6)	<0.0001
Bodily Pain	39.2 (19.8)	50.6 (25.1)	27.7 (15.2)	<0.0001
PCS	32.8 (9.5)	35.9 (8.5)	30.2 (7.9)	<0.0001
MCS	50.3 (10.4)	37.5 (11.7)	37.4 (11.2)	<0.0001
Mean Sheehan Disability (score range 0–10)	3.7 (2.9)	5.5 (2.7)	6.4 (2.5)	<0.0001
Mean overall quality of life (score range 0–10)	7.1 (2.2)	5.2 (1.8)	5.2 (2.3)	<0.0001
Mean GAD-7 anxiety (score range 0–21)	3.7 (3.9)	8.2 (5.5)	9.9 (5.9)	<0.0001
Mean disability days in past four weeks				
Bed days	2.7 (5.0)	5.0 (7.2)	7.7 (8.5)	<0.0001

(Continued)

Table 1  
Continued

Baseline Characteristics	Pain Only (n = 96)	Depression Only (n = 131)	Depression and Pain (n = 178)	P-value
Days activities reduced by $\geq 50\%$	9.5 (9.7)	11.5 (9.0)	11.9 (8.5)	0.096
Total disability days	12.2 (10.4)	16.5 (10.2)	19.6 (9.2)	<0.0001

SD = standard deviation.

\*Baseline medication data were available from the oncology medical records for 396 (97.8%) of the 405 participants, including 95 of 96 of those with pain, 126 of 131 of those with depression, and 175 of 178 of those with both pain and depression.

had a strong association ( $P < 0.0001$ ) with all five measures, whereas pain had a weaker but significant association with three measures: SF general health perceptions ( $P = 0.049$ ), overall quality of life ( $P = 0.048$ ), and total disability days in the past four weeks ( $P = 0.049$ ).

#### Self-Reported Health Care Use

Health care use in the preceding three months is summarized in Table 4. Although it was not surprising that nearly all patients had outpatient visits, the sheer volume of visits was impressive, with 31.6% of the patients having three to five outpatient visits, 28.4% having six to 10 visits, and 25.6% having more than 10 visits. In terms of more costly resources, 38% of patients reported at least one hospitalization in the past three months, with the total hospital days being one to two days in 8.7% of the study sample, three to five days in 9.7%, six to 10 days in 11.6%, and more than 10 days in 7.9%. One-third (33.1%) of the study patients reported at least one ED visit, with one of six (16.8%) reporting multiple ED visits. In contrast, a minority (17.8%) of patients reported any mental health visits during the preceding three months (defined as “psychiatrists, psychologists, social workers, psychiatric nurses, or counselors”). Even among the 309 patients with depression, less than one in five ( $n = 61$ , 19.7%) had seen a mental health professional. Finally, visits to CAM providers (defined as “alternative health care providers such as chiropractors, acupuncturists, massage therapists, or others”) were rare (only 4.7% of patients). There were no significant differences among the three symptom subgroups in their use of any of the categories of health care services.

#### Discussion

Our study has several important findings. First, of more than 4400 questionnaires

administered to patients in 16 oncology practice sites, nearly half screened positive for pain and/or depression of at least moderate severity, confirming the high prevalence of these two symptoms in cancer populations.<sup>1–3</sup> Second, pain and depression frequently co-occur and are synergistic in their association with impairment; 44% of our sample had comorbid depression and pain, and this subgroup had the worst quality of life and disability. The high comorbidity of pain and depression and their reciprocal adverse effects on one another and on quality of life and functioning has been reported for cancer<sup>54–56</sup> and other medical populations.<sup>57</sup> Third, our sample experienced marked disability both in terms of profound activity limitations (i.e., an average of 60% of days in the past four weeks spent either in bed or with activities reduced by at least 50%) and 43% reporting unemployment because of health reasons. Fourth, our sample had substantial health care use, but a low use of specialty care for depression and pain, meaning that the oncologist and/or patient’s primary care physician are the de facto principal provider of symptom-based care for cancer patients.

The distribution of cancer type and phase was similar among our three patient groups (i.e., pain only, depression only, and comorbid pain and depression). Previous research has shown that depression and other psychological symptoms are prevalent regardless of site of cancer<sup>9</sup> and vary more by prognosis, disease burden, and other factors rather than by specific type of cancer.<sup>58</sup> Likewise, pain was distributed across the spectrum of cancer phases from newly diagnosed to maintenance or disease free to recurrent or progressive. Thus, general screening for pain and depression in oncology practice is probably warranted rather than a narrow focus on certain subgroups of cancer patients.

The first step to better management of cancer-related symptoms is increased detection.



Table 2  
Depression and Pain-Specific Treatments Reported by Study Subjects

Treatment	Pain Only (n = 96)	Depression Only (n = 131)	Pain and Depression (n = 178)
Depression treatments		N (%)	
St. John's Wort or other herbals			
Ever	9 (9.4)	23 (17.6)	25 (14.0)
Mental health professional			
Ever	39 (40.6)	47 (35.9)	83 (46.6)
Current	4 (4.2)	16 (12.2)	24 (13.5)
Pain treatments		n (%)	
Pain treatments (can include more than 1)			
Over-the-counter medications	35 (36.5)	31 (23.7)	61 (34.3)
Prescribed medications	71 (74.0)	59 (45.0)	151 (84.8)
Nonpharmacological treatments	0 (0.0)	0 (0.0)	1 (0.6)
No pain treatments	3 (3.2)	58 (44.3)	4 (2.3)
Hours of relief from pain medicines (of 329 with analyzable data)	(n = 90)	(n = 71)	(n = 168)
0-1	5 (5.6)	10 (14.1)	16 (9.5)
2-3	17 (18.9)	7 (9.9)	47 (28.0)
4	26 (28.9)	15 (21.1)	37 (22.0)
5-12	36 (40.0)	26 (36.6)	58 (34.5)
>12	6 (6.7)	13 (18.3)	10 (6.0)
Specialists seen specifically for pain, and when			
Pain clinic			
Ever	20 (20.8)	17 (13.0)	35 (19.7)
Current	5 (5.2)	4 (3.1)	12 (6.7)
Physical therapy			
Ever	46 (47.9)	65 (49.6)	98 (55.1)
Current	7 (7.3)	3 (2.3)	15 (8.4)
Chiropractor			
Ever	40 (41.7)	58 (44.3)	68 (38.2)
Current	2 (2.1)	3 (2.3)	5 (2.8)
Massage therapy			
Ever	24 (25.0)	17 (13.0)	43 (24.2)
Current	4 (4.2)	1 (0.8)	12 (6.7)
Acupuncture			
Ever	6 (6.3)	7 (5.3)	9 (5.1)
Current	1 (1.0)	1 (0.8)	0 (0.0)
Orthopedic surgeon			
Ever	32 (33.3)	47 (35.9)	72 (40.5)
Neurologist			
Ever	28 (29.2)	30 (22.9)	58 (32.6)
Rheumatologist			
Ever	13 (13.5)	12 (9.2)	31 (17.4)
Another specialist for pain			
Ever	5 (5.2)	13 (9.9)	25 (14.0)
Nonpharmacological treatments			
Ever	9 (9.4)	14 (10.7)	18 (10.1)

The depression screener used in our study was the PHQ-2, which screens for the two core symptoms of depressive disorders, that is, depressed mood and anhedonia.<sup>26</sup> Ultrabrief screeners have been validated for depression in general,<sup>59</sup> including in cancer patients.<sup>60</sup> Also, ultrabrief screeners ranging from one to three items are validated for pain.<sup>61</sup> However, patients and physicians often expect the other party to

initiate discussions about symptoms and quality-of-life issues.<sup>62</sup> Therefore, educating physicians to ask about pain, depression, and other cancer symptoms and coaching and empowering patients to report such symptoms are essential.

Depression and pain had moderate to strong associations with impairment across multiple domains of quality of life and

Table 3  
**Association of Depression and Pain with HRQL and Disability: Results from Multivariable Regression Models**

HRQL or Disability Domain <sup>b</sup>	Strength of Association of Depression (HSCL-20) and Pain (BPI) Severity with HRQL/Disability <sup>a</sup>					
	Separate Models for Depression and Pain (Steps 1 and 2)		Combined Model with Both Depression and Pain (Step 3)		Combined Model Adjusted for Covariates (Step 4)	
	Standardized Beta or Chi-Square	P-value	Standardized Beta or Chi-Square	P-value	Standardized Beta or Chi-Square	P-value <sup>c</sup>
SF General Health Perceptions						
Depression	-5.45	<0.0001	-5.04	<0.0001	-3.97	<0.0001
Pain	-3.82	0.0002	-3.23	0.0013	-2.41	0.049
SF Vitality						
Depression	-14.29	<0.0001	-14.22	<0.0001	-14.27	<0.0001
Pain	-1.12	0.27	0.52	0.61	-0.43	0.67
Quality of life, overall						
Depression	-10.21	<0.0001	-10.53	<0.0001	-9.58	<0.0001
Pain	1.03	0.30	2.54	0.012	2.61	0.048
Sheehan Disability Index						
Depression	12.76	<0.0001	12.42	<0.0001	11.29	<0.0001
Pain	3.35	0.0009	2.26	0.024	1.82	0.14
Total disability days in past four weeks						
Depression	433.0	<0.0001	404.3	<0.0001	302.1	<0.0001
Pain	37.0	<0.0001	10.3	0.0013	6.3	0.049

<sup>a</sup>Association of each HRQL or disability domain with depression and pain was examined in multivariable models in four steps: association with depression alone (Step 1) and pain alone (Step 2) in separate models, with depression and pain together in combined model (Step 3), and with depression and pain adjusted for covariates of age, sex, race, medical comorbidity, education, income, and employment status (Step 4).

<sup>b</sup>Generalized linear regression (GLM) modeling was conducted for the two SF domains, Sheehan Disability Index, and quality of life. Poisson regression modeling was conducted for total disability days. Standardized beta is beta coefficient from regression model divided by its standard error and is value reported for GLM models. Chi-square is reported for Poisson models (which is only for total disability days).

<sup>c</sup>Adjusted for multiple comparisons using modified Bonferroni procedure.

functional status. Depression tended to have somewhat stronger effects than pain, and depression-pain comorbidity yielded the greatest impairment. The relationship between symptom burden and quality of life in cancer patients has been noted,<sup>6</sup> as has the particularly strong effects of depression.<sup>63,64</sup> The frequent co-occurrence of pain and depression (45% in our sample) and their additive adverse effects make them an especially pernicious symptom dyad.<sup>21</sup> Indeed, the clustering of cancer symptoms has attracted increasing attention, with pain, depression, and fatigue being a particularly triangulated cluster.<sup>56,65</sup>

Beyond a simple decrement in quality of life and functional status, our study demonstrated a considerable degree of frank disability. Patients reported more than 60% of their days in bed or with marked reductions in activity and a 43% health-related unemployment rate. Apart from cancer, depression and pain are two of the most common causes of decreased work productivity.<sup>66,67</sup> A recent meta-analysis showed the unemployment rate in cancer patients to be more than twice that of controls (34% vs. 15%).<sup>68</sup> Thus, one would expect that adding depression and/or pain

to the already disabling effects of cancer itself would be especially deleterious. At the same time, cancer patients experience substantial barriers to obtaining disability benefits.<sup>69</sup>

Health care use did not differ by symptom group in our study. The considerable amount of health care use in our study exemplifies the high financial burdens associated with cancer care, which includes not only direct medical expenses<sup>70</sup> but also indirect costs such as out-of-pocket expenditures,<sup>71</sup> as well as patient and caregiver time.<sup>72</sup> The National Cancer Institute estimated that the total direct medical costs associated with cancer diagnosis and treatment in the United States in 2004 was \$72.1 billion, whereas the indirect costs were even larger at \$118 billion.<sup>73</sup> Despite high health care use by patients in our trial, their self-reported treatments suggested a rather low rate of treatments specific to depression and pain, including only a small proportion of patients accessing mental health or pain specialists and many patients reporting insufficient relief from pain medications. This suggests that oncology services may continue to focus principally on treatment of the cancer itself with much less attention paid to symptoms

Table 4  
Patient-Reported Health Care Use in the Past Three Months in INCPAD Participants by Pain and Depression Subgroup<sup>a</sup>

Health Care Use Variable	Number of Visits or Days											
	0		1		2		3–5		6–10		>10	
	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)
Outpatient visits (n = 402)	2		24		33		127		114		103	
Pain only (n = 95)	0	(0.0)	9	(9.5)	10	(10.5)	33	(34.7)	26	(27.4)	17	(17.9)
Depression only (n = 131)	1	(0.8)	4	(3.1)	13	(9.9)	39	(29.8)	36	(27.5)	38	(29.0)
Pain and depression (n = 176)	1	(0.6)	11	(6.3)	9	(5.1)	55	(31.3)	52	(29.5)	48	(27.3)
Hospital days (n = 404)	251		24		11		39		47		32	
Pain only (n = 96)	62	(64.6)	4	(4.2)	4	(4.2)	10	(10.4)	9	(9.4)	7	(7.3)
Depression only (n = 131)	82	(62.6)	5	(3.8)	2	(1.5)	14	(10.7)	15	(12.2)	13	(9.9)
Pain and depression (n = 177)	107	(60.5)	15	(8.5)	5	(2.8)	15	(8.5)	23	(13.0)	12	(6.8)
ED visits (n = 405)	271		66		31		30		7		0	
Pain only (n = 96)	73	(76.0)	11	(11.5)	4	(4.2)	7	(7.3)	1	(1.0)	0	(0.0)
Depression only (n = 131)	95	(72.5)	18	(13.7)	10	(7.6)	6	(4.6)	2	(1.5)	0	(0.0)
Pain and depression (n = 178)	103	(57.9)	37	(20.8)	17	(9.6)	17	(9.6)	4	(2.2)	0	(0.0)
Mental health visits (n = 405)	333		25		21		12		8		6	
Pain only (n = 96)	85	(88.5)	2	(2.1)	6	(6.3)	2	(2.1)	1	(1.0)	0	(0.0)
Depression only (n = 131)	109	(83.2)	10	(7.6)	7	(5.3)	3	(2.3)	1	(0.8)	1	(0.8)
Pain and depression (n = 178)	139	(78.1)	13	(7.3)	8	(4.5)	7	(3.9)	6	(3.4)	5	(2.8)
CAM visits (n = 405)	386		3		3		7		4		2	
Pain only (n = 96)	92	(95.8)	0	(0.0)	2	(2.1)	2	(2.1)	0	(0.0)	0	(0.0)
Depression only (n = 131)	127	(96.9)	1	(0.8)	0	(0.0)	1	(0.8)	2	(1.5)	0	(0.0)
Pain and depression (n = 178)	167	(93.8)	2	(1.1)	1	(0.6)	4	(2.2)	2	(1.1)	2	(1.1)

<sup>a</sup>There were no significant differences among the three symptom groups for any of the five measures of health care use, either in unadjusted analyses or in analyses adjusted for multiple comparisons using a modified Bonferroni procedure.

that accompany the cancer or its treatment. Although some patients may access CAM care, CAM was used by only a fraction of our patients and nationally accounts for only a small percent of cancer expenditures.<sup>74</sup>

Once detected, pain and depression must be effectively treated. Approaches for managing cancer-related pain include evidence-based analgesic algorithms,<sup>75</sup> patient education<sup>76,77</sup> and coaching,<sup>78</sup> improving clinician knowledge and attitudes,<sup>79–81</sup> addressing patient and clinician misconceptions about cancer pain and its treatment,<sup>82–84</sup> and increasing patient adherence.<sup>85</sup> Regarding depression and other psychological conditions, there is modest evidence for pharmacological and psychotherapeutic interventions,<sup>86–89</sup> although more definitive evidence from larger clinical trials is needed.<sup>90</sup> Among psychotherapeutic interventions, cognitive-behavioral therapy<sup>91</sup> and problem-solving therapy<sup>92</sup> seem particularly promising. Given the context and competing demands of busy oncology practices, collaborative care interventions, which have consistently proven effective for depression in general medical settings,<sup>93</sup> might be an

efficient strategy for cancer-related symptom management. Indeed, a collaborative telecare management approach covering multiple oncology practices is the focus of our present trial.<sup>25</sup>

Our study has several limitations. The cross-sectional nature of our data prevents us from establishing a causal effect of depression and pain on the substantial functional impairment, decreased quality of life, and high health care use found in our study participants. However, there is considerable evidence that depression and pain individually do worsen these health outcomes, and that in combination have additive ill effects.<sup>21,55,57</sup> Second, INCPAD enrolled a broad range of patients both by type and phase of cancer. This is a study strength in terms of generalizability to oncology practice but limits our ability to draw definitive conclusions about depression and pain in any one type or phase of cancer. Third, most data were obtained by patient self-report, which is the criterion standard for symptoms, such as depression and pain, and functional status and quality of life domains, but may be less desirable for health care use. The latter is

available from automated records in large integrated health care systems but is not feasibly obtained in a statewide trial such as INCPAD that involves individual rural and urban community-based oncology practices. Self-report correlates reasonably well with actual health care use<sup>94</sup> and has been relied on in previous community-based depression trials.<sup>95</sup> Although it may introduce some measurement imprecision into absolute rates of health care use, it is less likely to bias between-group comparisons.

In summary, depression and pain are prevalent across a wide range of cancer types and phases and are associated with increased disability and diminished HRQL. Compared with pain, depression tends to have a somewhat greater and more pervasive effect across multiple domains. This may be because of a number of factors ranging from depression being especially impairing to it being less readily recognized or treated by oncologists to greater reluctance by patients to accept a depression diagnosis or treatment. The frequent co-occurrence of depression and pain, as well as their additive effects in several domains, suggests that the detection of one symptom should trigger inquiry about the other. Our INCPAD trial will address the degree to which impairment is reduced by the comanagement of pain and depression.

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