Title

Differences in Demographic, Clinical, and Symptom Characteristics and Quality of Life Outcomes Among Oncology Patients with Different Pain Experiences

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Differences in Demographic, Clinical, and Symptom Characteristics and Quality of Life Outcomes Among Oncology Patients with Different Pain Experiences

by

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ABSTRACT

The purposes of this study in oncology outpatients receiving chemotherapy (CTX), were to describe the occurrence of different types of pain (i.e., no pain, only cancer pain, only non-cancer pain, or both cancer and non-cancer pain) and to evaluate for differences in demographic, clinical, and symptom characteristics, as well as quality of life (QOL) among the four groups. Patients completed self-report questionnaires to evaluate demographic and symptom characteristics as well as QOL. Medical records were reviewed for disease and treatment information. Of the 926 patients in this study, 27.5% were categorized in the no pain group and 72.5% reported pain. Of the 671 who reported pain, 15.6% reported only non-cancer pain, 26.8% only cancer pain, and 30.1% both cancer and non-cancer pain. Across the three groups with pain, severity scores were in the moderate to severe range. Compared to the no pain group, patients with both cancer and non-cancer pain were significantly younger, more likely to be female, have a higher level of comorbidity and a poorer functional status. In addition, these patients reported higher levels of depressive symptoms, anxiety, fatigue, sleep disturbance, decrements in energy, and attentional fatigue, as well as poorer QOL outcomes. Patients with only non-cancer pain were significantly older than the other three groups. The most common comorbidities in the non-cancer pain group were back pain, hypertension, osteoarthritis, and depression. Unrelieved cancer pain continues to be a significant problem. Patients need to be assessed for both cancer and non-cancer pain conditions.

Key words:

cancer pain; non-cancer pain; pain prevalence; chemotherapy; fatigue; depression; anxiety, sleep disturbance; quality of life

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INTRODUCTION

Pain is one of the most prevalent and distressing symptoms for cancer patients. Over 30 years ago, Bonica attempted to evaluate the worldwide prevalence of cancer pain.[1] In this historic publication that evaluated pain in 15 countries, the mean pain prevalence rate in oncology patients across various stages of the disease was 50%. In patients with advanced, metastatic, or terminal cancer, the average prevalence rate was 71%.

Since that publication,[1] a variety of organizations, including the World Health Organization,[2] the Agency for Health Care Policy and Research,[3] the American Pain Society,[4] and the National Comprehensive Cancer Network,[5] have disseminated guidelines on the assessment and management of cancer pain. The overall goal of all of these guidelines is to reduce the burden of cancer pain for patients and their family caregivers.

Despite the identification of unrelieved cancer pain as a major public health problem and major attempts to improve its management, a number of recent systematic reviews have documented the extent of this ongoing clinical problem.[6-8] In one meta-analysis that focused on the prevalence of cancer pain,[6] data from 52 studies were evaluated. Pooled prevalence rates for pain were as follows: 33% in patients after curative treatment; 59% in patients undergoing active treatment; and 64% in patients in the advanced or terminal phases of their illness. Across all cancer types, the pooled prevalence rate for pain was 53%. Of note, 33% of the patients rated their pain as moderate or severe.

The other two systematic reviews were focused on the undertreatment of cancer pain.[7,8] In the 2008 review that evaluated studies that used the Pain Management Index scores[9] to estimate the undertreatment of cancer pain,[7] the authors concluded that 43% of oncology patients were undertreated (range 8% to 82%). Predictors of undertreatment included date of study publication before 2001; some provenances located in Europe or Asia; countries with a gross national income per capita of <$40,000; and a care center that was not focused on oncology patients. In this review, age was not a significant predictor of undertreatment. In the

update of this review, published in 2014,[8] an additional 20 articles were evaluated. Over the six year period (i.e., 2007 to 2013), the authors concluded that cancer pain management improved by 25% (i.e., from a 43% rate of undertreatment to 32%). Again, lower national income and nonspecific setting for cancer treatment were associated with higher levels of undertreatment.

Notably absent from these reviews is a systematic evaluation of the types of pain that oncology outpatients experience while undergoing cancer treatment. A fundamental principle of effective pain management is to determine the cause of the pain. However, no studies were identified that evaluated the prevalence of cancer pain, non-cancer pain, and both cancer and non-cancer pain in patients undergoing cancer treatment. This type of evaluation is particularly important given the increased number of older adults with cancer[10-12] and the increased number of comorbid conditions in patients with cancer.[13, 14]

An equally important consideration in the evaluation of the pain experience of oncology patients is its association with other common symptoms. Several studies have documented that pain can co-occur with fatigue,[15, 16] sleep disturbance,[15-17] anxiety,[15-17] and depressive symptoms[15-18] in oncology patients undergoing CTX. However, none of these studies documented the severity of these symptoms in oncology patients with different types of pain.

Finally, the identification of risk factors associated with different types of pain and the impact of different types of pain on patients' quality of life (QOL) will assist clinicians to perform more comprehensive assessments of pain in oncology outpatients. Given the limited amount of information on the occurrence of pain, its association with other common symptoms, and its impact on QOL, the purposes of this study in a sample of oncology outpatients receiving chemotherapy (CTX, n=926), were to describe the occurrence of different types of pain (i.e., no pain, only cancer pain, only non-cancer pain, or both cancer and non-cancer pain) and to evaluate for differences in demographic, clinical, and symptom characteristics, as well as QOL outcomes among the four pain groups.

PATIENTS AND METHODS

Patients and Settings

This study is part of an ongoing, longitudinal study of the symptom experience of oncology outpatients receiving CTX. Eligible patients were ≥18 years of age; had a diagnosis of breast, gastrointestinal, gynecological, or lung cancer; had received CTX within the preceding four weeks; were scheduled to receive at least two additional cycles of CTX; were able to read, write, and understand English; and gave written informed consent. Patients were recruited from two Comprehensive Cancer Centers, one Veteran's Affairs hospital, and four community-based oncology programs. A total of 1528 patients were approached and 926 consented to participate (60.6% response rate). The major reason for refusal was being overwhelmed with their cancer treatment.

Instruments

A demographic questionnaire obtained information on age, gender, ethnicity, marital status, living arrangements, education, employment status, and income. Alcohol use was evaluated using the Alcohol Use Disorders Identification Test (AUDIT).[19]

The Karnofsky Performance Status (KPS) scale is widely used to evaluate functional status in patients with cancer and has well established validity and reliability. Patients rated their functional status using the KPS scale that ranged from 30 (I feel severely disabled and need to be hospitalized) to 100 (I feel normal; I have no complaints or symptoms).[20]

The Self-Administered Comorbidity Questionnaire (SCQ) is a short and easily understood instrument that was developed to measure comorbidity in clinical and health service research settings.[8] The questionnaire consists of 13 common medical conditions that were simplified into language that could be understood without any prior medical knowledge. Patients were asked to indicate if they had the condition; if they received treatment for it; and did it limit their activities. For each condition, a patient can receive a maximum of 3 points. Total scores can range from 0

to 39. The SCQ has well-established validity and reliability and has been used in studies of patients with a variety of chronic conditions.[21, 22]

Occurrence of pain was evaluated using the Brief Pain Inventory.[23] Patients who responded yes to the question about having pain were asked to indicate if their pain was or was not related to their cancer treatment. Patients were categorized into one of four groups (i.e., no pain, only noncancer pain, only cancer pain, both cancer and noncancer pain). Patients rated the intensity of the pain (i.e., now, average, worst) using 0 (none) to 10 (excruciating) numeric rating scales (NRS). In addition, they provided information on the length of time they were in pain, how often their pain occurred, locations of their pain, quality of the pain, pain's level of interference with function, and their level of pain relief and satisfaction with pain treatment.

The Lee Fatigue Scale (LFS) consists of 18 items designed to assess physical fatigue and energy.[24] Each item was rated on a 0 to 10 NRS. Total fatigue and energy scores were calculated as the mean of the 13 fatigue items and the 5 energy items, with higher scores indicating greater fatigue severity and higher levels of energy. Patients were asked to rate each item based on how they felt "right now," within 30 minutes of awakening (i.e., morning fatigue, morning energy) and prior to going to bed (i.e., evening fatigue, evening energy). Cutoff scores of $\geq$3.2 and $\geq$5.6 indicated high levels of morning and evening fatigue, respectively.[25] Cutoff scores of $\leq$6.0 and $\leq$3.5 indicate low levels of morning and evening energy, respectively. The LFS was chosen for this study because it is relatively short, easy to administer, and has well established validity and reliability.[24, 26] In this study, Cronbach's alphas for evening and morning fatigue at enrollment were 0.95 and 0.96, respectively. Cronbach's alphas for evening and morning energy were 0.93 and 0.95, respectively.

The Spielberger State-Trait Anxiety Inventories (STAI-T and STAI-S) consist of 20 items each that are rated from 1 to 4. The scores for each scale are summed and can range from 20 to 80. Cutoff scores of $\geq$31.8 and $\geq$32.2 indicate high levels of trait and state anxiety, respectively. The STAI-S and STAI-T inventories have well established validity and

reliability.[27,28] In the current study, the Cronbach's alphas for the STAI-T and STAI-S were 0.92 and 0.96, respectively.

The Center for Epidemiological Studies-Depression scale (CES-D) consists of 20 items selected to represent the major symptoms in the clinical syndrome of depression. A total score can range from 0 to 60, with scores of ≥16 indicating the need for individuals to seek clinical evaluation for major depression. The CES-D has well established validity and reliability.[29, 30] In the current study, the Cronbach's alpha for the CES-D total score was 0.89.

The Pittsburgh Sleep Quality Index (PSQI) consists of 19 items designed to assess the quality of sleep in the past month. The global PSQI score is the sum of the seven component scores. The global PSQI score ranges from 0 to 21 with higher scores indicate a higher level of sleep disturbance. A global PSQI score of >5 indicates a significant level of sleep disturbance.[31] The PSQI has well established validity and reliability.[31-33] In this study, the Cronbach's alphas for the global PSQI score was 0.72.

The General Sleep Disturbance Scale (GSDS) consists of 21-items designed to assess the quality of sleep in the past week. Each item was rated on a 0 (never) to 7 (everyday) NRS. The GSDS total score is the sum of the seven subscale scores that can range from 0 (no disturbance) to 147 (extreme sleep disturbance). A higher score indicates higher levels of sleep disturbance. A GSDS total score of ≥43 indicates a significant level of sleep disturbance.[34] The GSDS has well-established validity and reliability.[34, 35] In the current study, the Cronbach's alpha for the GSDS total score was 0.83.

The Attentional Function Index (AFI) consists of 16 items designed to measure attentional function.[36] A higher total mean score on a 0 to 10 NRS indicates greater capacity to direct attention. Scores are grouped into categories of attentional function (i.e., <5.0 low function, 5.0 to 7.5 moderate function, >7.5 high function). The AFI has well established reliability and validity.[36] In this study, the Cronbach's alpha for the total AFI score was 0.93.

Quality of life was evaluated using a generic (i.e., Medical Outcomes Study-Short Form-12 (SF-12))[37] and a disease-specific (i.e., Quality of Life Scale-Patient Version (QOL-PV))[38, 39] measure. The SF-12 consists of 12 questions about physical and mental health as well as overall health status. The individual items on the SF-12 are evaluated and the instrument is scored into two components that measure a physical component summary (PCS) and a mental component summary (MCS). These scores can range from 0 to 100. Higher PCS and MCS scores indicate a better QOL. The SF-12 has well established validity and reliability.[37]

The QOL-PV is a 41-item instrument that measures four dimensions of QOL (i.e., physical, psychological, social, and spiritual well-being) in cancer patients, as well as a total QOL score. Each item is rated on a 0 to 10 NRS with higher scores indicating a better QOL. The QOL-PV has established validity and reliability.[38, 39] In the current study, the Cronbach's alpha for the QOL-PV total score was 0.92.

Study Procedures

The study was approved by the Committee on Human Research at the University of California, San Francisco and by the Institutional Review Board at each of the study sites. Eligible patients were approached by a research staff member in the infusion unit to discuss participation in the study. Written informed consent was obtained from all patients. Depending on the length of their CTX cycles, patients completed questionnaires in their homes, a total of six times over two cycles of CTX (i.e., prior to CTX administration (i.e., recovery from previous CTX cycle), approximately 1 week after CTX administration (i.e., acute symptoms), approximately 2 weeks after CTX administration (i.e., potential nadir)). For this analysis, data from the enrollment assessment, that asked patients to report on their pain experience for the week prior to the administration of the next cycle of CTX, were analyzed. Medical records were reviewed for disease and treatment information.

Data Analysis

Data were analyzed using SPSS version 22 (IBM, Armonk, NY). Descriptive statistics and frequency distributions were calculated for demographic and clinical characteristics. Differences in demographic, clinical, and symptoms characteristics, as well as QOL outcomes, were evaluated using analysis of variance (ANOVA), Chi Square tests, and Kruskal-Wallis tests with Bonferroni corrected post hoc contrasts. A p-value of <.05 was considered statistically significant. All calculations used actual values. Adjustments were not made for missing data. Therefore, the cohort for each of these analyses was dependent on the largest set of complete data among the pain groups.

RESULTS

Occurrence rates for pain group membership

Of the 926 patients in this study, 27.5% were categorized in the no pain group and 72.5% of these patients reported pain. Of the 671 patients who reported pain, 15.6% reported only non-cancer pain, 26.8% reported only cancer pain, and 30.1% reported both cancer and non-cancer pain.

Differences in demographic and characteristics among the pain groups

As shown in Table 1, differences were found among the pain groups in age, gender, education, marital status, living situation, childcare responsibilities, employment status, and income. Patients with only non-cancer pain were significantly older than the other three groups. Patients with no pain were significantly older than patients with only cancer pain. Compared to the no pain group, female patients were significantly more likely than males to report both cancer and non-cancer pain. Compared to patients with no pain, patients with both cancer and non-cancer pain were less likely to be married or partnered, more likely to live alone, less likely to be employed, and more likely to have an annual household income of <$30,000. Additional between-group post hoc comparisons are listed in Table 1.

Differences in clinical characteristics among the pain groups

A number of clinical characteristics differed among the pain groups (Table 1). Compared to the no pain and only non-cancer pain groups, patients in the only cancer pain and both cancer and non-cancer pain groups had lower KPS scores. In terms of number of comorbidities, all of the pain groups had a higher number of comorbidities than the no pain group. In terms of SCQ scores, the differences among the groups were as follows: no pain < only cancer pain < only non-cancer pain < both cancer and non-cancer pain. The occurrence of a number of comorbidities differed among the pain groups. Compared to the no pain group, a higher percentage of patients in the non-cancer pain and both cancer and non-cancer pain groups had high blood pressure. Compared to the no pain group, a higher percentage of patients in the non-cancer pain group had lung disease. Compared to the other three pain groups, a higher percentage of patients in the cancer and non-cancer pain group reported ulcer or stomach disease. Compared to both the no pain and only non-cancer pain groups, a higher percentage of patients with both cancer and non-cancer pain reported anemia and depression. A higher percentage of patients with non-cancer pain and both cancer and non-cancer pain reported osteoarthritis compared to the other two pain groups. The patterns of occurrence for back pain were as follows: no pain < the other three pain groups and only cancer pain < non-cancer pain and both cancer and non-cancer pain groups.

Differences in pain severity ratings among the three pain groups

For pain now and worst pain, patients with both cancer and non-cancer pain reported significantly higher scores than the only non-cancer and only cancer pain groups. For average pain, patients with both cancer and non-cancer pain reported higher scores than patients with only cancer pain.

Differences in symptom severity scores among the pain groups

Table 2 summarizes the differences in severity ratings for depression, anxiety, sleep disturbance, fatigue, energy, and attentional function among the four pain groups. In terms of CES–D scores, compared to the no pain group, patients with only cancer pain and both cancer

and non-cancer pain reported significantly higher scores. In addition, patients with both cancer and non-cancer pain had higher CES-D scores than patients with only non-cancer or only cancer pain.

In terms of STAI-T scores, compared to the no pain group, patients in the other three pain groups had significantly higher scores. In addition, patients with both cancer and non-cancer pain had higher STAI-T scores than patients with only non-cancer or only cancer pain. In terms of STAI–S scores, the post hoc comparisons were identical to those found for the CES-D scores.

In terms of the sleep disturbance measures, the post hoc contrasts for the GSDS scores were identical to those found for the CES-D and the STAI-S scores. In terms of PSQI scores, patients in the only cancer pain and both the cancer and non-cancer pain groups had significantly higher scores, than patients in the other two pain groups.

The patterns for the post hoc contrasts for morning and evening fatigue differed among the pain groups. For morning fatigue, patients with only cancer pain or both cancer and non-cancer pain had significantly higher scores than the other two pain groups. In addition, patients with both cancer and non-cancer pain had higher morning fatigue scores than patients with only cancer pain. In terms of evening fatigue, compared to patients with no pain, patients with only cancer pain or both cancer and non-cancer pain reported higher scores.

The patterns for the post hoc contrast for morning and evening energy were identical. Compared to the no pain group, patients with only cancer pain and both cancer and non-cancer pain reported significantly lower morning and evening energy scores.

In terms of the AFI scores, the post hoc contrasts were identical to those found for the STAI-T scores.

Differences in QOL scores among the pain groups

The subscale and summary scores for the SF-12 are listed in Table 3. For the physical functioning, general health, social functioning, role emotional, and mental health scores, the

post hoc contrasts revealed an identical pattern (i.e., only cancer pain and both cancer and non-cancer pain < no pain, as well as both cancer and non-cancer pain < only non-cancer and only cancer pain). For the role physical scale, compared to patients with no pain or only non-cancer pain, patients in the other two pain groups had lower scores. For bodily pain and the PCS scores, the post hoc contrasts revealed an identical pattern (i.e., both cancer and non-cancer pain < only cancer pain < only non-cancer pain < no pain). For the vitality score, patients in the only cancer or both cancer and non-cancer pain groups had lower scores that the no pain group. In terms of MCS scores, compared to the other three pain groups, patients with both cancer and non-cancer pain had lower scores.

The subscale and total scores for the QOL-PV are summarized in Table 3. For the physical and social well-being subscales, post hoc contrasts revealed an identical pattern (i.e., only cancer pain and both cancer and non-cancer pain < no pain and only non-cancer pain). For psychological well-being, compared to patients with no pain, patients with only cancer or both cancer and non-cancer pain reported lower scores. In addition, compared to patients with only non-cancer and only cancer pain, patients with both cancer and non-cancer pain reported lower scores. In terms of total QOL scores, compared to patients with no pain or only non-cancer pain, patients with only cancer and both cancer and non-cancer pain reported lower scores. In addition, compared to patients with only cancer pain, patients with both cancer and non-cancer pain reported lower total QOL scores.

DISCUSSION

This study is the first to provide detailed occurrence rates for various types of pain in a large sample of oncology outpatients receiving CTX. In addition, differences in the severity of common symptoms and QOL outcomes among these pain groups were evaluated. The discussion is organized based on the major findings from this study.

Pain occurrence rates and severity scores

In this study, over 70% of patients receiving CTX reported pain that was in the moderate to severe range. This occurrence rate is higher than the 59% reported in a recent systematic review[6] and may be partially explained by the inclusion of non-cancer pain in the current analysis (i.e., 16% of the sample). In addition, this occurrence rate is significantly higher than the 38% reported by patients at the initiation of RT.[40] In this RT study, 34.3% of the patients attributed their pain to only cancer, 49.3% to other medical conditions, and 16.4% to both cancer and other medical conditions. These differences in percentage rates for types of pain in oncology patients may be related to the higher percentage of patients with prostate cancer who were receiving primary treatment with RT and the lower percentage of patients with metastatic disease. Of note, in the current study, the occurrence rates for only cancer pain and both cancer and non-cancer pain were approximately equal. Taken together, over 60% of this sample had non-cancer pain. This finding suggests that clinicians need to assess for multiple types of pain in oncology outpatients and that the types of pain may vary depending on the treatment setting and patients' stage of disease.

In terms of pain severity, an expected patients with both cancer and non-cancer pain reported the highest severity scores for pain now, as well as for average and worst pain. Moreover, for the three pain groups, worst pain severity scores were in the moderate to severe range.[41-43] In fact, 29.9% of the patients with only non-cancer pain, 27.0% with only cancer pain, and 46.5% with both cancer and non-cancer pain reported worst pain scores in the severe range (i.e., >7). This finding suggests that both cancer and non-cancer pain continue to be undertreated despite the dissemination of numerous clinical practice guidelines.[2-5]

Demographic characteristics that differentiated among the pain groups

Age was one of the characteristics that differentiated among the pain groups. Of note, patients with only non-cancer pain were significantly older than the other three pain groups. This association between increased age and non-cancer pain may be partially explained by the higher number of comorbidities and the higher SCQ score in the only non-cancer pain group.

This hypothesis is supported by the relatively high occurrence rates for osteoarthritis (22.9%), back pain (38.2%), and rheumatoid arthritis (8.3%) reported by patients in the only non-cancer pain group.

In terms of gender differences in pain group membership, the only significant post hoc contrast was for a higher percentage of females being in the both cancer and non-cancer pain group compared to the no pain group. While several chronic pain conditions have higher prevalence rates in females (e.g., migraine headache,[44, 45] osteoarthritis[46]), findings regarding gender differences in cancer pain are inconsistent with some studies reporting no differences [47, 48] and others reporting higher rates in females.[49-51]

In terms of social characteristics, compared to patients with no pain or only cancer pain, a higher percentage of patients with both cancer and non-cancer pain were single and lived alone. Consistent with prior research,[52-54] lack of social support may play an important role in increasing patients' pain experiences.

While over 50% of the total sample was not employed, compared to the no pain and only cancer pain groups, a lower percentage of the patients in the both cancer and non-cancer pain group, were employed. In addition, the patients with both cancer and non-cancer pain reported lower household incomes overall. These findings may be partially explained by the significant disability associated with persistent pain and the poorer functional status of this pain group. Additional research is warranted on the impact of pain on the employment status of oncology patients receiving CTX.

Clinical characteristics that differentiated among the pain groups

Only three clinical characteristics (i.e., comorbidities, KPS score, number of prior cancer treatments) differentiated among the pain groups. As noted above, and consistent with previous reports,[55] a higher level of comorbidity was reported by patients in the only non-cancer pain and the both cancer and non-cancer pain groups. Based on the specific comorbidities evaluated using the SCQ, osteoarthritis, back pain, and rheumatoid arthritis were the most common

painful conditions reported by these two pain groups. In addition, approximately 30% of the patients in the both cancer and non-cancer pain group reported the occurrence of depression. Equally important approximately 40% of the patients in the only non-cancer and both cancer and non-cancer pain groups reported hypertension, which is known to increase pain severity in a variety of persistent pain conditions (for review see [56]).

An equally important clinical characteristic that differentiated among the pain groups was KPS score. In this sample, patients with only cancer pain and both cancer and non-cancer pain had significantly lower KPS scores than patient in the other two pain groups. Of note, these differences in functional status scores for the two pain groups compared to both the no pain (d=0.63 to 0.79) and only non-cancer pain groups (d=0.57) represent clinically meaningful differences in KPS scores.[57, 58]

In terms of number of prior cancer treatments, compared to patients with no pain, patients with both cancer and non-cancer pain had received a higher number of cancer treatments. Prior cancer treatments, including surgery, radiation therapy, and CTX may contribute to the development of persistent pain including: post-surgical pain syndromes,[59-62] as well as radiation,[63, 64] and CTX-induced[65, 66] neuropathies. Additional research is warranted to determine the specific etiologies for the cancer pain reported by patients undergoing CTX.

Differences in common symptoms among the pain groups

Consistent with previous reports in patients with cancer[67, 68] and non-cancer pain,[69-71] the occurrence of moderate to severe pain is associated with a higher symptom burden. However, no studies were identified that reported on associations between pain and six of the most common symptom experienced by oncology patients (i.e., depressive symptoms, anxiety, sleep disturbance, fatigue, decrements in energy, attentional fatigue) in the same patients receiving CTX. In terms of depressive symptoms, and consistent with previous reports,[15-18] depressive symptoms differentiated among the pain groups. While the no pain group reported low CES-D scores, patients with only non-cancer pain and only cancer pain reported subsyndromal levels

of depressive symptoms.[72-74] Not surprising, patients with both cancer and non-cancer pain reported CES-D scores above the clinically meaningful cutoff score. In addition, this latter group of patients reported the highest occurrence rate for depression (i.e., 29.4%) on the SCQ. Of note, the percentages of patients in this study who had subsyndromal (~42%) and clinically meaningful (~30%) levels of depressive symptoms is higher than percentages found in a study of patients at the initiation of RT (i.e., ~15% and ~5.2%, respectively).[73] Taken together, these findings suggest that clinicians need to assess for the co-occurrence of depressive symptoms in oncology patients who report pain.

Consistent with previous reports,[15-17] anxiety is a common and distressing symptom for patients receiving CTX. Across the three groups with pain, both the trait and state anxiety scores were above the clinically meaningful cutoff scores. However, patients with both cancer and non-cancer pain had the highest trait and state anxiety scores. Potential reasons for the higher scores in this group include that these patients were younger, had a higher level of comorbidities, and were living alone.

In terms of sleep disturbance, all four groups had GSDS and PSQI scores that were above the clinically meaningful cutoff scores. While the receipt of CTX is known to produce sleep disturbance,[75, 76] patients with pain had higher scores than the no pain group. Of note, the sleep disturbance scores of the patients with only cancer pain and both cancer and non-cancer pain were comparable to those reported by shift workers.[34] While comparisons across studies are difficult due to differences in the measures used to assess sleep disturbance, in a study of pain and sleep disturbance in patients at the initiation of RT,[40] GSDS and PSQI scores for patients in the no pain group in the current study (i.e., 45.53 and 6.76, respectively) were slightly higher the scores reported by patients in the RT study (i.e., 37.20 and 6.07, respectively). However, for the other three pain groups in the current study, the GSDS and PSQI scores were higher than in the RT study (i.e., 46.27 and 7.64, respectively). However, it should be noted that in both studies, patients in pain reported sleep disturbance scores about clinically meaningful cutpoints.

In a similar fashion, patients receiving CTX report high levels of fatigue.[32,33,68] Only a limited number of studies have reported on diurnal variations in fatigue severity[33] and none were identified that evaluated the relationship between pain and diurnal variations in fatigue. In a study of patients at the initiation of RT, that used the LFS, mean morning fatigue scores were 2.38,[77] which is comparable to patients in the no pain group. However, in the current study, the remaining three groups reported higher morning fatigue scores. In addition, patients with only cancer pain and both cancer and non-cancer pain reported scores that were above the clinically meaningful cutoff and were significantly greater than the other two groups. Since these patients were evaluated prior to receiving their next dose of CTX, these between group differences suggest that cancer pain is associated with increases in morning fatigue in patients receiving CTX. Since pain is known to disrupt sleep,[33] these relatively high levels of morning fatigue may be related to the higher levels of both pain and sleep disturbance reported by these patients.

In terms of evening fatigue, patients at the initiation of RT reported mean scores of 4.23.[77] All four groups of patient in the current study reported higher evening fatigue scores. However, only patients in the both cancer and non-cancer pain group reported evening fatigue scores that were above the clinically meaningful cutoff. Again, patients with only cancer and both cancer and non-cancer pain reported higher evening fatigue scores than the no pain group. Taken together, the findings for both morning and evening fatigue suggest that pain, as well as sleep disturbance, contribute to higher levels of morning and evening fatigue in patients undergoing CTX.

No studies were identified that evaluated the relationships between pain and diurnal variations in energy levels. Recent evidence from our research group[78] and from studies of patients with HIV disease[79] suggests that decrements in energy levels are a distinct symptom from fatigue. In our study of patients at the initiation of RT, ratings of morning and evening energy using the LFS were 5.73 and 4.48, respectively.[77] For all four groups of patients in the current study, morning and evening energy scores were lower.

In the current study, even though patients in the only cancer pain and both cancer and non-cancer pain groups, compared to the no pain group, reported significant decrements in morning energy, none of the groups scores were below the clinically meaningful cutoff. In contrast, all of the groups' evening energy scores were below the clinically meaningful cutoff. Similar to morning energy, patients with only cancer and both cancer and non-cancer pain reported the lowest evening energy scores. Given the limited amount of information on diurnal variations in energy levels in oncology patients receiving CTX, these findings warrant confirmation in future studies.

Patients receiving CTX report decreases in cognitive function.[80-82] No studies were identified that evaluated the effects of pain on cognitive function in patients receiving CTX. However, AFI scores for patients in the current study were slightly lower that scores of patients at the initiation of RT[83] or prior to breast cancer surgery.[84] In all four pain groups, their AFI scores were in the moderate range which suggests decrements in cognitive function.[36] Again, compared to the no pain group, the other three groups had significantly lower AFI scores. These decrements in attentional function could be due to the CTX itself,[80-82] the high level of sleep disturbance these patients were experiencing,[85, 86] and/or the pain itself or the use of analgesic medications.[87]

Differences in QOL outcomes among the pain groups

In the current study, generic (i.e., SF-12) and disease-specific (i.e. QOL-PV) measures Of QOL were used to evaluate the impact of pain on QOL outcomes. As shown in Table 3, while all of the SF-12 subscale scores were lower than in healthy individuals,[37] compared to the no pain group, patients in the other three groups had poorer outcomes. In general, the differences in SF-12 subscale scores between the no pain group and the other three groups represent clinically meaningful differences in QOL (see effect size calculations on Table 3).[57, 58] An evaluation of the PCS and MCS scores, with 50 being the normative score for the general United States population,[37] suggests that while both scores are below the normative value, the

occurrence of pain has a larger impact on patients' physical functioning than on their mental functioning.

In terms of the disease specific measure of QOL, the subscale and total QOL scores reported by patients in the current study are similar to those reported by patients with colon[88] and ovarian[89] cancer, as well as by patients with breast colon, lung, or prostate cancer who participated in a intervention study that aimed to decrease pain and fatigue.[90] Similar to the SF-12 scores, most of the differences between the no pain and the other three pain groups represent clinically meaningful differences in QOL. It should be noted that the patients with both cancer and no-cancer pain had the worst outcomes using both measures of QOL.

Study limitations

Several study limitations need to be acknowledged. First, detailed information on the exact causes of both cancer and non-cancer pain were not evaluated. In addition, while the sample size was large, the percentages of male patients and patients who were members of ethnic minority groups were relatively small. Therefore, findings regarding gender differences and the lack of ethnic differences among the pain groups may not generalize to all oncology patients receiving CTX. In addition, data on specific symptom management interventions are not available for these patients.

Clinical implications and directions for future research

Findings from this study demonstrate that unrelieved pain remains a significant problem for oncology patients receiving CTX. In general, in those patients who report pain, depressive symptoms, anxiety, sleep disturbance, fatigue, and decrements in energy, and decrements in attentional function are worse than in oncology patients without pain. Future studies need to evaluate the exact etiologies of both cancer and non-cancer pain in these patients as well as the common and distinct mechanisms that contribute to the increased symptom burden and poorer QOL outcomes. In addition, intervention studies are warranted that evaluate the impact of single or multimodal interventions on these common co-occurring symptoms. Until new treatments are

available for these co-occurring symptoms, clinicians need to do a detailed assessment of each symptom and develop the optimal treatment plan for each patient.

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Table 1. Differences in Demographic and Clinical Characteristics Among the Pain Groups (n = 926)

Characteristic	No Pain (1) n = 255 27.5%	Only Non-Cancer Pain (2) n = 144 15.6%	Only Cancer Pain (3) n = 248 26.8%	Both Cancer & Non-Cancer Pain (4) n = 279 30.1%	Statistics
	Mean (SD)	Mean (SD)	Mean (SD)	Mean (SD)	
Age (years)	58.57 (11.79)	62.16 (11.56)	54.75 (11.15)	56.16 (12.24)	F=13.99; p<.0001 1 > 3 2 > 1, 3, and 4
Education (years)	16.38 (3.05)	16.18 (3.10)	16.61 (2.92)	15.75 (2.96)	F=3.85; p=.009 3 > 4
Body mass index (kg/m^2)	25.77 (5.60)	26.39 (6.44)	26.01 (5.26)	26.39 (5.93)	F=0.65; p=.584
Karnofsky Performance Status score	85.65 (10.39)	82.98 (11.62)	78.03 (11.31)	76.07 (12.44)	F=34.02; p<.0001 1 and 2 > 3 and 4
Number of comorbidities	1.76 (0.92)	2.81 (1.48)	2.08 (1.21)	3.05 (1.54)	F=53.20; p<.0001 1 < 2, 3, and 4 2 and 4 > 3
SCQ score	4.03 (1.94)	6.01 (3.16)	4.89 (2.54)	7.03 (3.64)	F=53.63; p<.0001 1 < 3 < 2 < 4
AUDIT score	2.97 (2.14)	2.46 (1.86)	3.10 (2.86)	2.75 (2.23)	F=1.78; p=.150
Time since cancer diagnosis (years)	1.74 (3.16)	2.57 (3.97)	2.30 (4.10)	2.40 (4.92)	KW; p=.089
Time since cancer diagnosis (median)	0.40	0.69	0.44	0.47	
Number of prior cancer treatments	1.50 (1.41)	1.94 (1.62)	1.76 (1.53)	1.80 (1.58)	F=2.99; p=.030 1 < 2
Number of metastatic sites including lymph node involvement	1.12 (1.62)	1.33 (1.24)	1.27 (1.28)	1.38 (1.32)	F=2.05; p=.106
Number of metastatic sites excluding lymph node involvement	0.69 (1.00)	0.87 (1.07)	0.82 (1.09)	0.92 (1.16)	F=2.10; p=.099
	% (N)	% (N)	% (N)	% (N)	
Gender Female+ Male Transgender*	 72.5 (185) 27.5 (70) 0.0 (0)	 82.6 (119) 16.7 (24) 0.07 (1)	 77.4 (192) 22.6 (56) 0.0 (0)	 84.6 (236) 15.4 (43) 0.0 (0)	χ^2=13.61; p =.003 4>1
Ethnicity White Black Asian or Pacific Islander Hispanic Mixed or Other	 74.1 (186) 6.8 (17) 11.2 (28) 8.0 (20)	 78.6 (110) 5.7 (8) 10.0 (14) 5.7 (8)	 69.4 (170) 8.6 (21) 13.1 (32) 9.0 (22)	 66.3 (179) 7.0 (19) 12.2 (33) 14.4 (39)	χ^2=13.71; p=.133
Married or partnered (% yes)	74.6 (188)	65.0 (93)	71.5 (176)	56.0 (154)	χ^2=24.04; p<.0001 1 and 3 > 4
Lives alone (% yes)	16.7 (42)	21.0 (30)	16.3 (40)	27.3 (76)	χ^2=12.90; p=.005 4 > 1 and 3
Child care responsibilities (% yes)	22.9 (58)	11.4 (16)	25.2 (61)	26.5 (72)	χ^2=13.16; p=.004 1, 3 and 4 > 2
Care of adult responsibilities (% yes)	7.5 (18)	8.6 (11)	5.3 (12)	11.8 (30)	χ^2=7.07; p=.070
Currently employed (% yes)	43.7 (111)	31.7 (45)	39.0 (96)	25.3 (70)	χ^2=22.40; p<.0001 1 and 3 > 4
Income					KW; p<.0001

< $30,000+ $30,000 to <$70,000 $70,000 to < $100,000 ≥ $100,000	10.5 (24) 18.4 (42) 17.1 (39) 53.9 (123)	17.9 (22) 26.8 (33) 13.8 (17) 41.5 (51)	10.2 (23) 20.4 (46) 19.6 (44) 49.8 (112)	29.4 (74) 23.4 (59) 14.7 (37) 32.5 (82)	4 > 1 and 3 2 > 1
Specific comorbidities (% yes)					
Heart disease	3.9 (10)	6.2 (9)	4.4 (11)	7.2 (20)	χ^2=3.46; p=.327
High blood pressure	24.3 (62)	38.2 (55)	25.4 (63)	36.9 (103)	χ^2=17.07; p=.001 2 and 4 > 1 and 4 > 3
Lung disease	7.8 (20)	18.1 (26)	9.7 (24)	14.3 (40)	χ^2=11.97; p=.007 2 > 1
Diabetes	5.9 (15)	11.8 (17)	7.3 (18)	9.7 (27)	χ^2=5.32; p=.150
Ulcer or stomach disease	2.0 (5)	1.4 (2)	2.0 (5)	9.7 (27)	χ^2=29.67; p<.0001 4 > 1, 2, and 3
Kidney disease	0.8 (2)	1.4 (2)	0.4 (1)	1.1 (3)	χ^2=1.24; p=.743
Liver disease	4.3 (11)	4.9 (7)	7.7 (19)	6.1 (17)	χ^2=2.86; p=.413
Anemia or blood disease	7.8 (20)	9.7 (14)	9.7 (24)	19.0 (53)	χ^2=19.10; p<.0001 4 > 1 and 3
Depression	11.4 (29)	19.4 (28)	17.7 (44)	29.4 (82)	χ^2=28.28; p<.0001 4 > 1 and 3
Osteoarthritis	3.9 (10)	22.9 (33)	5.2 (13)	20.4 (57)	χ^2=60.60; p<.0001 2 and 4 > 1 and 3
Back pain	4.3 (11)	38.2 (55)	16.5 (41)	47.0 (131)	χ^2=149.60; p<.0001 2, 3, and 4 > 1 2 and 4 > 3
Rheumatoid arthritis	0.8 (20)	8.3 (12)	2.0 (5)	5.4 (15)	χ^2=19.07; p<.0001 2 and 4 > 1 2 > 3
Exercise on a regular basis (% yes)	76.8 (195)	66.7 (96)	67.2 (166)	65.7 (180)	χ^2=9.32; p=.025 1 > 4
Smoking, current or history of (% yes)	36.8 (93)	35.5 (50)	31.4 (76)	38.4 (106)	χ^2=2.95; p=.399
Cancer diagnosis Breast Gastrointestinal Gynecological Lung	 40.4 (103) 30.2 (77) 15.3 (39) 14.1 (36)	 40.3 (58) 27.1 (39) 14.6 (21) 18.1 (26)	 1.9 (104) 28.2 (70) 21.8 (54) 8.1 (20)	 39.4 (110) 25.1 (70) 22.6 (63) 12.9 (36)	χ^2=15.51; p=.078
Type of prior cancer treatment No prior treatment Only surgery, CTX, or RT Surgery & CTX, or Surgery & RT, or CTX & RT Surgery & CTX & RT Surgery & CTX & RT	 23.7 (59) 43.8 (109) 19.7 (49) 12.9 (32)	 20.6 (29) 32.6 (46) 31.2 (44) 15.6 (22)	 18.9 (46) 46.7 (114) 20.1 (49) 14.3 (35)	 20.2 (56) 42.2 (117) 21.3 (59) 16.2 (45)	χ^2=13.48; p=.142

Abbreviations: AUDIT = Alcohol Use Disorders Identification Test, CTX = chemotherapy, kg = kilograms, KW = Kruskal Wallis; m^2 = meter squared, RT = radiation therapy, SCQ = Self-Administered Comorbidity Questionnaire, SD = standard deviation

*Chi Square analysis and post hoc contrasts done without the transgender patient include in the analyses
+Reference group for the post hoc comparisons

Table 2. Differences in Symptom Severity Scores Among the Pain Groups (n = 926)

Characteristic	No Pain (1) n = 255 27.5%	Only Non-Cancer Pain (2) n = 144 15.6%	Only Cancer Pain (3) n = 248 26.8%	Both Cancer & Non-Cancer Pain (4) n = 279 30.1%	Statistics
	Mean (SD)	Mean (SD)	Mean (SD)	Mean (SD)	
Symptom Scores					
Center for Epidemiological Studies – Depression Scale score	9.28 (7.66)	11.28 (9.03)	13.20 (9.00)	16.64 (10.71)	F=29.31; p<.0001 1 < 3 and 4 2 and 3 < 4
Trait Anxiety Inventory score	31.07 (9.03)	34.50 (10.67)	35.06 (9.95)	39.53 (11.17)	F=30.13; p<.0001 1 < 2, 3, and 4 2 and 3 < 4
State Anxiety Inventory score	29.75 (10.60)	32.38 (12.30)	33.59 (11.41)	37.89 (13.71)	F=20.34; p<.0001 1 < 3 and 4 2 and 3 < 4
General Sleep Disturbance score	45.53 (18.51)	49.84 (19.87)	53.75 (19.87)	59.44 (19.55)	F=23.40; p<.0001 1 < 3 and 4 2 and 3 < 4
Pittsburgh Sleep Quality Index score	6.76 (3.50)	7.09 (3.78)	8.13 (3.61)	9.22 (4.00)	F=22.04; p<.0001 1 and 2 < 3 and 4
Morning fatigue score	2.23 (1.89)	2.67 (2.01)	3.31 (2.09)	3.87 (2.31)	F=29.49; p<.0001 1 and 2 < 3 and 4 3 < 4
Evening fatigue score	4.88 (2.17)	5.11 (2.01)	5.52 (2.03)	5.67 (2.08)	F=7.43; p<.0001 1 < 3 and 4
Morning energy score	4.99 (2.33)	4.40 (2.28)	4.42 (2.11)	3.97 (2.10)	F=9.33; p<.0001 1 > 3 and 4
Evening energy score	3.89 (2.09)	3.56 (1.92)	3.35 (1.93)	3.39 (2.06)	F=3.64; p=.013 1 > 3 and 4
Attentional Function Index score	7.06 (1.70)	6.54 (1.60)	6.33 (1.75)	5.74 (1.76)	F=25.84; p<.0001 1 > 2, 3, and 4 2 and 3 > 4
Pain Scores					
Pain now	n/a	1.45 (1.88)	1.47 (1.88)	2.22 (2.17)	F=10.19; p<.0001 2 and 3 < 4
Average pain score	n/a	2.90 (1.94)	2.67 (1.84)	3.41 (2.02)	F=8.38; p<.0001 3 < 4
Worst pain score	n/a	5.41 (2.67)	5.54 (2.56)	6.75 (2.33)	F=17.54; p<.0001 2 and 3 < 4

Abbreviations: n/a = not applicable, SD = standard deviation

Table 3. Differences in Quality of Life Scores Among the Pain Groups (n = 926)

Characteristic	No Pain (1) n = 255 27.5%	Only Non-Cancer Pain (2) n = 144 15.6%	Only Cancer Pain (3) n = 248 26.8%	Both Cancer & Non-Cancer Pain (4) n = 279 30.1%	Statistics
	Mean (SD)	Mean (SD)	Mean (SD)	Mean (SD)	
MOS-SF-12 (SF-12) Subscale and Summary Scores					
Physical functioning	63.28 (32.19)	55.08 (33.96) [0.24]	48.61 (33.74) [0.43]	40.64 (33.25) [0.66]	F=20.72; p<.0001 1 > 3 and 4 2 and 3 >4
Role physical	63.40 (29.24)	57.76 (27.58) [0.19]	49.74 (28.70) [0.47]	43.75 (27.34) [0.67]	F=23.30; p<.0001 1 and 2 > 3 and 4
Bodily pain	95.60 (12.90)	81.57 (21.50) [0.51]	73.13 (26.99) 0.82]	60.37 (28.74) [1.29]	F=99.65; p<.0001 1 > 2 > 3 >4
General health	73.51 (23.87)	67.45 (24.89) [.022]	60.46 (28.66) [0.47]	53.58 (28.20) [0.72]	F=26.11, p<.0001 1 > 3 and 4 2 and 3 > 4
Vitality	53.59 (25.44)	46.51 (27.58) [0.26]	42.36 (27.11) [0.42]	39.74 (25.28) [0.52]	F=13.60; p<.0001 1 > 3 and 4
Social functioning	76.99 (24.62)	73.72 (29.29) [0.11]	65.73 (30.43) [0.37]	57.46 (33.10) [0.64]	F=21.16; p<.0001 1 > 3 and 4 2 and 3 > 4
Role emotional	83.37 (24.28)	79.32 (24.83) [0.15]	75.42 (27.30) [0.29]	67.17 (28.96) [0.59]	F=17.08; p<.0001 1 > 3 and 4 2 and 3 > 4
Mental health	78.24 (18.03)	73.18 (20.87) [0.24]	71.33 (20.88) [0.38]	65.11 (22.16) [0.62]	F=18.11; p<.0001 1 > 3 and 4 2 and 3 > 4
SF-12 – Physical component summary score	46.50 (8.57)	43.09 (9.25) [0.33]	39.65 (10.36) [0.66]	36.98 (10.20) [0.92]	F=43.61; p<.0001 1 > 2 > 3 > 4
SF-12 – Mental component summary score	51.44 (9.36)	49.97 (10.81) [0.14]	48.94 (10.29) [0.24]	46.36 (11.12) [0.48]	F=10.27; p<.0001 1, 2, and 3 > 4
Multidimensional QOL-Cancer Subscale and Total Scores					
Physical well-being	7.50 (1.57)	7.20 (1.52) [0.17]	6.14 (1.74) [0.76]	5.93 (1.71) [0.88]	F=52.05; p<.001 1 and 2 > 3 and 4
Psychological well-being	6.23 (1.72)	5.85 (1.86) [0.20]	5.36 (1.76) [0.47]	4.77 (1.81) [0.78]	F=31.44; p<.001 1 > 3 and 4 2 and 3 >4
Social well-being	6.63 (1.79)	6.25 (1.91) [0.19]	5.28 (1.82) [0.67]	4.93 (2.02) [0.84]	F=42.46; p<.001 1 and 2 > 3 and 4
Spiritual well-being	5.37 (2.11)	5.23 (2.02)	5.32 (2.03)	5.04 (2.09)	F=0.64; p=.59
Total QOL score	6.41 (1.32)	6.07 (1.38) [0.23]	5.49 (1.36) [0.63]	5.15 (1.42) [0.86]	F=41.41; p<.001 1 and 2 > 3 and 4 3 > 4

Numbers in brackets below the mean scores are effect size calculations that compare the no pain group to each of the other three pain groups.

Abbreviations: MOS-SF-12 = Medical Outcomes Study – Short Form 12 (SF-12), n/a = not applicable, QOL = quality of life, SD = standard deviation

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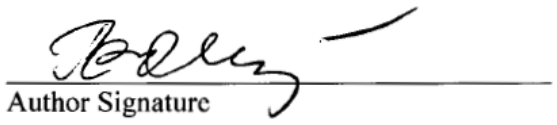

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