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Distinguishing Features of Cancer Patients Who Smoke: Pain, Symptom Burden, and Risk for Opioid Misuse

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Abstract

Although many cancer patients who have pain are smokers, the extent of their symptom burden and risk for opioid misuse are not well understood. In this study we analyzed records of patients being treated for cancer pain, 94 of whom were smokers and 392 of whom were non-smokers, to determine smoking status group differences. Smokers had significantly higher pain intensity, fatigue, depression, and anxiety than non-smokers (Independent samples t-tests P <0.002). Smokers were at higher risk for opioid misuse based on the short form of the Screener and Opioid Assessment for Patients with Pain (SOAPP). Specifically, smokers endorsed more frequent problems with mood swings, taking medications other than how they are prescribed, history of illegal drug use and history of legal problems (Chi-square tests $P \leq 0.002$). Changes in pain and opioid use were examined in a subset of patients (146 non-smokers and 46 smokers) who were receiving opioid therapy on at least two of the three data time points (consult, follow-up 1 month after consult, follow-up 6-9 months after consult). Results based on multilevel linear modeling showed that over a period of approximately 6 months, smokers continued to report significantly higher pain than non-smokers. Both smokers and non-smokers reported a significant decline in pain across the six-month period; the rate of decline did not differ across smokers and non-smokers. No significant difference over time was found in opioid use between smokers and non-smokers. These findings will guide subsequent studies and inform clinical practice, particularly the relevancy of smoking cessation.

Keywords

Smoking; cancer pain; opioids

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Introduction

The prevalence of pain among patients receiving active cancer treatment is 24-60% [40]. Among patients with advanced cancer, 58-69% report moderate to very severe pain (1). Despite challenging side effects and risk of misuse, opioid therapy remains a principal treatment for cancer pain [33]. Previous studies suggest smokers experience more pain and other negative symptoms than non-smokers and are at greater risk for opioid misuse [11,13, 15, 17, 21, 25, 27, 29, 32, 43, 44].

Smoking is a risk factor for 18 different cancers [2, 24]. Approximately 90% of all lung cancer cases are attributable to cigarette smoking [23]. Compared to never-smokers, cigarette smokers have a 10-fold increase in risk for head and neck cancer [10, 38]. It is estimated that between one half and three quarters of all cancer patients are current smokers at the time their cancer is diagnosed [2, 24] . Despite the importance of smoking cessation, as many as half of these patients continued to smoke during and after their cancer treatment [10, 20, 23]. For those who continue to smoke despite a cancer diagnosis, there may be impaired wound healing, reduced treatment efficacy, increased risk of postoperative complications, increased risk for developing another primary cancer and decreased chance of survival [4, 5, 12, 26, 31, 27, 39].

Although many symptoms that typically burden patients with cancer have not been investigated by smoking status, persistent smoking is known to exacerbate dyspnea and fatigue [15]. Smokers with a diagnosis of lung cancer report higher pain levels than those who have never smoked and those who have stopped smoking [11]. Among those with different cancer diagnoses, current smokers reported higher pain levels and higher need for opioids than non-smokers, with no differences found across subgroups of former smokers and those who never smoked [15]. In a study of patients who were newly diagnosed with head and neck cancer, current smokers reported higher pain and pain-related interference than did former smokers and those who never smoked [29].

Among smokers who do not have cancer, preliminary data suggest a relation between recurrent pain and tobacco use. Smoking has been associated with the development and aggravation of low back pain and musculoskeletal pain [1, 18, 19, 34, 42]. Smokers who experience situational or recurrent pain report greater motivation to smoke and increase cigarette consumption [13, 17, 21, 25]. A recent article identified altered processing of pain, interaction with opioids, psychosocial factors, and depression as some potential mechanisms relating chronic pain and smoking [36]. Another study found that baseline depression and clinical pain were greater among current smokers compared to former and never smokers. When multivariate analyses were performed, pain severity was associated with greater depression but not smoking; however, smoking was associated with greater opioid use, independent of depression [22].

Differences in opioid use by smoking status have been reported in patients without cancer. Specifically, smokers who do not have cancer report more frequent requirement for postoperative opioids [36]. An increased likelihood of high-dose opioid use has been reported among patients with chronic non-cancer pain who smoke [32]. Findings of an inverse relation between serum levels of some oral opioids (viz., propoxyphene, hydrocodone with acetaminophen) with serum nicotine levels have led some researchers to conclude that cigarette smoking decreases opioid efficacy [43, 36]. A possible explanation for smokers' need for increased opioids is that opioid analgesic efficacy may be reduced because the stimulant actions of nicotine counter the analgesic properties of opioids [43, 36] . Another explanation is that the polycyclic aromatic hydrocarbons (PAHs) in tobacco smoke induce drug metabolizing enzymes, thus decreasing the analgesic effect of opioids and requiring a higher

effective dose [27, 22]. Experimental studies in mice demonstrate that nicotine pretreatment induces cross-tolerance to morphine requiring higher opioid doses to achieve the same antinocioceptive effect as can be achieved in non-tolerant animals [43].

Our primary aim was to investigate the extent to which pain intensity and a broad array of other symptoms differ across smokers and non-smokers with cancer. A secondary aim was to investigate the extent of differences in risk factors for opioid misuse across smoking status. Another secondary aim was to investigate pain and opioid use patterns over time and across smoking status. These areas of research have not been adequately addressed among cancer patients. Collectively, the clinical, epidemiological, and experimental studies discussed led to our expectation of higher pain ratings and other symptom burden among patients who smoke and have cancer-related pain versus those who do not smoke. Because smoking has been implicated as a potentially relevant risk factor for opioid misuse among patients with chronic non-cancer pain [30], we expected this relation among patients with cancer. We also expected smokers would continue to have higher pain and opioid use over time.

Methods

Sample

This is a retrospective study on data that were obtained from the records of 522 consecutive new patients seen at the Pain Management Center of The University of Texas MD Anderson Cancer Center from 01/01/09 to 06/30/09. The study was approved by the IRB. Being a new patient at the pain center from the stated time period was the inclusion criterion. Exclusion criteria were not providing smoking status (28 patients), being under the age of 21 or not providing age (6 patients), and not providing smoking status or age (2 patients). The resulting sample included 94 current smokers and 392 non-smokers (former smokers and never smokers were not studied separately as significant differences among them had not been found in prior studies). Demographic and clinical data are in Table 1.

To study changes in pain and opioid use over time, a subset of patients (146 non-smokers and 46 smokers) from the study sample was selected. Inclusion criteria for this subset were having opioid and pain data for at least 2 of 3 time points. The 3 time points were initial consult at the pain center, 1st follow-up occurring (2-6 weeks after consult, and long-term follow-up occurring within 6-9 months after first consult. A footnote describing the subset of patients appears in Table 4. Opioid use was calculated in morphine equivalency daily dose (MEDD; See Appendix 1 for Conversion Formula) milligrams based on the sum of long- and short-acting opioids used per day.

Measures

As part of the pain center standard assessment, all patients complete a rating of their usual pain in the past week from the Brief Pain Inventory (BPI) [9]. A symptom assessment inventory based on a modified version of the Edmonton Symptom Assessment Scale (ESAS) [6, 8] was used to capture ratings of fatigue, shortness of breath, poor appetite, depression, anxiety, drowsiness, difficulty thinking clearly and insomnia in the past week. Both the BPI and the ESAS use an 11-point rating scale where 0 = none and 10 = worst imaginable.

Item-level responses from the 5-item Short Form Version.1 of the Screener and Opioid Assessment for Patients with Pain (SOAPP-SF) were used as indictors of opioid misuse risk [7]. Item-level data were used instead of the total score because there was low internal consistency among the items (Coefficient alpha = .51). The SOAPP-SF response scale ranges from 0 = Never to 4 = Very Often. After analyzing stem and leaf plots of the item-

level data, we collapsed the response scale to be 0 = Never, 1 and 2 = Infrequently, and 3 and 4 = Often. We investigated response differences on the SOAPP items probing mood swings, misuse of medication, use of illegal drugs, and lifetime legal problems across smokers and non-smokers. The remaining SOAPP-SF item (the second item on the scale) assesses frequency of smoking within an hour after awakening. Response pattern on this SOAPP-SF item was investigated only for current smokers.

At the time of the initial pain center consult, opioid use was assessed by a clinic nurse who had a face to face meeting with the patient and asked about the amount of average daily opioids medication used in the past week. At subsequent time points, opioid use was based on the amount prescribed by the pain center physician. Current smoking status was obtained from consult notes that were also made by a pain center nurse at the time of the patient's consult appointment at the pain center.

Analyses of Data

SAS was used for all analyses of data. We used independent samples t-tests to make comparisons between smokers and non-smokers on continuous variables that included age, usual pain and other symptom ratings at the time of the initial consult. Chi-square tests were used to make statistical comparisons between smokers and non-smokers on categorical variables that included gender, employment status, cancer diagnosis, and individual SOAPP-SF indicators of opioid misuse risk.

To investigate differences in smoking status on pain and opioid use over time and in relation to depression and anxiety, we examined usual pain rating and patients' opioid use across three clinic visits at the pain center. The repeated measures design of these examinations produced responses that were nested within participants that could be characterized by the two-level structure of a multilevel model. Multilevel linear modeling (MLM; 40) was used to estimate the effects of smoking status and visits on pain and opioid use. Specifically, we constructed two separate MLMs, the first one regressing pain on smoking status and visits and the second one regressing opioid use on smoking status and visits. Analyses of an intercept-only model (i.e., a model with no predictors) found that an unstructured covariance structure provided the best fit with the correlation structure in the data set. A standard approach to model building was followed and predictors were initially entered as fixed-effect predictors. To assess whether the slopes characterizing the relationship between visit and the outcome variables (e.g., pain or opioid use) varied among participants, we added the random slope coefficients for visits to the model. We used a log-likelihood ratio test to evaluate whether adding a random slope coefficient significantly improved the goodness-of-fit of a model over one without its inclusion.

Results

Table 1 outlines the patient characteristics of this sample at the time of the initial consult to the pain center by smoking status. On average, smokers were significantly younger than non-smokers. A significant difference was also found for employment status across smoking status. A higher percentage of the smokers were disabled, whereas a higher percentage of the non-smokers were retired. The difference in overall distribution of cancer diagnoses across smoking status was assessed and found not to be statistically significant. Although some specific cancer diagnoses appear to be notably different (e.g., more smokers had head and neck cancers than non-smokers), these were not compared individually.

Table 2 shows that smokers reported significantly higher pain, fatigue, poor appetite, depression, anxiety, and insomnia than non-smokers. Although the differences in shortness

of breath and drowsiness were not statistically significant, smokers reported slightly higher symptom ratings of problems with these symptoms than non-smokers.

Table 3 presents data on opioid misuse risk indicators by smoking status. Chi-square tests show significant differences between smokers and non-smokers on response patterns of occurrence of mood swings, taking medication other than the way it was prescribed, history of illegal drug use, and history of legal problems or arrest. Visual inspection of response patterns shows a higher percentage of non-smokers than smokers reported never having mood swings (27.9% of non-smokers versus 18.1% of smokers) whereas a higher percentage of smokers versus non-smokers endorsed having mood swings often (26.6% of smokers versus 12.5% of non-smokers). On the item pertaining to illegal drug use in the past 5 years, non-smokers reported endorsed “never” more than smokers (96.2% of non-smokers versus 80.8% of smokers), whereas smokers reported more “infrequent” use than non-smokers (13.8% of smokers versus 2.6% of non-smokers) and more “often” use than non-smokers (5.3% of smokers versus 1.3% of non-smokers). A similar response pattern on the item pertaining to legal problems or arrest was found. Specifically, non-smokers more than smokers reported “never” (91.6% of non-smokers versus 67% of smokers), whereas smokers reported more “infrequent” legal problems than non-smokers (25.5% of smokers versus 8.2% of non-smokers) and more “often” problems than non-smokers (3.2% of smokers versus 0.3% of non-smokers). We examined smokers’ responses on Item 2 of the SOAPP. This item probes frequency of smoking a cigarette within an hour after awakening. Findings are that 28% percent of the smokers endorsed “never,” 21% endorsed “infrequently,” and 51% endorsed “often.”

We constructed MLMs to examine the effects of smoking and visits on pain on the subset of patients who were on opioid therapy for at least two of the data collection time points. We found that a model with random slope effects for visits did not improve the model's fit over a model in which visits were treated as fixed effects. Using the latter model, we found a significant main effect for smoking status, F (1,190) =5.46,p<.05 and a significant main effect for visits F (1,263)=71.63,p<.0001 . No significant interaction effect between smoking status and visits was found. The results indicated that across the three clinic visits, smokers reported significant higher level of usual pain than non-smokers. Furthermore, both smokers and non-smokers reported a decline in usual pain across the three clinic visits. The analysis was repeated with age, gender, baseline level of depression, and baseline level of anxiety added as covariates, but the results were unaffected when controlling for these factors. These findings were consistent with an analysis performed using all available data to ensure that the missing data would not bias results and alter our conclusions. These results are also presented in Table 4.

Table 4 also shows the results examining the effects of smoking status and visits on opioid use. Using the best-fitting model that included visits as random effects, we did not find significant main effects for either smoking status or visits, nor did we find a significant interaction effect between smoking status and visits. That is, smokers and non-smokers alike used similar amounts of opioids across the three clinic visits. Although the results showed a trend towards higher opioid use across visits for the subset sample, the increase was not statistically significant. The analysis was repeated with age, gender, baseline level of depression, and baseline level of anxiety added as covariates, but the results were unaffected when controlling for these factors.

Discussion

The primary aim of the current study was to investigate differences in symptom burden across smoking status among patients with cancer pain across smoking status. As

hypothesized, smokers reported significantly more pain and other symptom burden than non-smokers. A secondary aim was to investigate opioid misuse risk across smoking status. As expected, smokers were at greater risk. Finally, on a subsample of patients on opioid therapy for at least two points of time, we sought to investigate changes in pain and opioid use patterns across smokers and non-smokers. As expected, pain continued to be higher among smokers. Although we had expected opioid use over time to be higher among smokers too, we found that smoking status was not related to opioid use.

These important findings expand understanding of smoking and cancer pain. Unlike previous studies [11, 15], ours included patients with differing cancer diagnoses and a broader range of symptom profiles than found in the literature[11, 15]. Our study also provided a fuller investigation of indictors of opioid misuse risk across smoking status. To our knowledge, pain and opioid use trajectories across smoking status have not been investigated previously.

The finding of smokers having more pain than non-smokers is consistent with previous studies among cancer patients [11, 15]. Due to the cross-sectional nature of these findings, we are unable to discern whether smoking may have increased pain or been motivated by the pain experience itself. Empirical support exists for both directions. Specifically, although true causal effects have not been established, research suggests that smoking may serve as a marker and/or risk factor for the incidence and severity of non-cancer chronic pain [13]. For example, it has been suggested that tobacco smoke may increase pain by reducing blood and oxygen flow to peripheral tissues, or via direct influence on the neurological processing of sensory information. Another explanation offered is that avoidance and relief of pain may be a potent reinforcer in the maintenance of tobacco dependence [14]. Further, the efficacy of pain medications may be affected by the potential interactions between selected pain medications and smoking [43, 36]. In support of this interpretation, experimentally manipulated pain has been found to increase smoking urge and decrease latency to smoke [13]. Moreover, interventions which reduce expectancies about the analgesic effects of smoking have been found to decrease urge and increase latency to smoke among smokers who undergo a cold pressor pain task [16].

The full spectrum and intensity of symptom burden that we found among smokers and non-smokers was not previously described in the cancer pain [11, 15] and non-cancer pain [36, 22] literature. Our findings show a profile of higher levels of physical symptoms (pain, fatigue, poor appetite, and insomnia) and psychological symptoms (depression and anxiety) among smokers than non-smokers. Our sample had higher ratings on fatigue as than on other symptoms. Shortness of breath, drowsiness, and difficulty thinking were not distinguishing symptoms across smokers and non-smokers. In particular, shortness of breath and difficulty thinking were not rated as highly problematic.

Opioid therapy is one of the most useful options for helping cancer patients manage their pain. Common challenges with opioid therapy include misuse potential as well as other side effects such as constipation, drowsiness, and difficulty thinking. Hence, we felt it was important to study potential differences in opioid misuse risk indicators across smoking status. Although the majority of smokers and non-smokers report never having mood swings, taking medication other than the way it was prescribed, having a history of illegal drug use, and having a history of legal problems or arrest, there were some notable smoking-status group response differences on each SOAPP-SF item. Smokers were more likely than non-smokers to report have problems on each SOAPP-SF item. Also of interest is that over half of all smokers indicated that they often smoke their first cigarette within an hour after awakening, which suggests that many patients who smoke exhibited a higher level of nicotine dependence.

Changes in pain and opioid use were examined using a subset of patients who were receiving opioid therapy on at least two of the three data time points (consult, 1st follow-up after consult which for the majority of patients was approximately 1 month after consult, long term follow-up within 6-9 months after first consult). Extending previous findings that looked at pain at a single time point, the current study showed that, over a period of approximately six months, smokers continued to report significantly higher level of pain than non-smokers. Furthermore, both smokers and non-smokers reported a significant decline in pain across the six-month period; the rate of decline did not differ across smokers and non-smokers. In contrast to the higher use of opioids among smokers that has been reported among cancer patients [1] and non-cancer patients [22], we did not find a significant difference in opioid use between smokers and non-smokers. Our data show that both groups received similar amount of opioid therapy from their physicians. Only at the long-term follow-up time point, did smokers receive more opioid therapy. However, because our focus was change in opioid use over time and also because this difference was based on a small sample of smokers, we chose not to test this difference for statistical significance. For smokers and non-smokers alike, an overall decline in reported pain was associated with a trend, albeit non-significant, of an increase in the amount of opioid therapy received.

The unique characteristics of our sample must be taken into account when interpreting the findings from this study. The smoker and non-smoker groups were not selected to be uniform across demographic and cancer diagnosis. Given that the sample was one of convenience, some differences by smoking status were expected. In our sample, on average, smokers were 4 years younger than non-smokers and there were some employment status differences and cancer diagnoses differences across groups as well. Although cancer diagnosis overall was not significantly different across smokers and non-smokers, in some specific diagnoses such as head and neck cancers we noted a higher prevalence of current smoking. These demographic and clinical differences may be interrelated with the variables of major interest in this study. In another example, diagnosis of cancer at a younger age and having strain from being disabled could adversely affect symptom burden and risk for opioid misuse, as well as being associated with higher smoking prevalence.

Other characteristic unique to the patients seen at our pain center must be taken into consideration. When new patients are referred to our center, the majority of them are already on opioid therapy as prescribed by their oncologist. Although our patients are at various stages of the disease process, the majority have advanced cancer and associated symptom burden. Most have dealt with pain before a referral is made to the pain center. An added stressor for some of our patients is that they may have relocated temporarily from various parts of the United States and beyond for their cancer care.

In addition to the unique characteristics of our sample, a limitation of this study is that non-smokers included both those who had never smoked and those who had quit. Many relations between pain and smoking are thought to be a function of smoking duration. There may be important benefits to quitting smoking that could only be captured by examining differences between current, former, and never smokers. Another limitation is that many participants did not have complete data at follow-up points. Therefore, the MLM analyses where based on a subset of participants.

With these considerations and limitation in mind, the results of this study provide support for the link between pain and smoking and suggest that among cancer patients, smokers report greater physical and psychological symptom burden. Recommendations based on these finding are for a comprehensive symptom assessment and treatment of pain and other symptoms. We also underscore the importance of smoking status in treatment planning. Smoking history, status, and level of nicotine dependence should be included in clinical and

research databases to enable further analyses of these topics and related questions. Future and larger studies should consider separating out never smokers and those who have quit. Although the causal direction between smoking and pain is unclear, a clinical interview which included assessment of smoking triggers and motivation and pain coping would help to inform treatment. For example, if expectation of analgesic benefit appeared to be an important smoking motivator, challenging these expectations and increasing coping self-efficacy would be reasonable treatment goals [16, 35]. If future studies confirm that smoking is associated with depression symptoms, treatment of depression would be appropriate [3]. Thus, matching treatment to the individual, with a careful consideration of smoking motivation and coping, should improve pain control and smoking cessation outcomes in cancer settings.

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Appendix

Appendix 1

MEDD Conversion Formula

Opioid with route and dose	Conversion factor	MEDD (mg)
Morphine p.o. 1 mg	1	1
Hydromorphone p.o. 1 mg	5	5
Oxycodone p.o. 1 mg	1.5	1.5
Methadone p.o. 1 mg	6	6
Methadone i.v. 1 mg	10	10
Fentanyl transdermal 1 μg/h	2	2
Tramadol	**0.2**	**0.2**
Hydrocodone	0.5	0.5
Meperidine	0.1	0.1

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Perspective

This article describes pain, symptom burden, and risk for opioid misuse among cancer patients with pain across smoking status. Smoking appears to be a potential mechanisms of having an increased pain and symptom burden and risk for opioid misuse. This improved understanding of cancer pain will inform clinical practice.

Table 1

Demographic and Clinical Characteristics of Participants by Smoking Status

	Smoking Status			
	Smoker[a]	**Non-Smoker**[a]	**p-value**	**Total N (col %)**
N	94	392		486
Gender, *n (row %)*				
Female	49 (19.4)	203 (80.6)	0.975[c]	252 (51.8)
Male	45 (19.2)	189 (80.8)		234 (48.2)
Age in years				
Mean (SD)	51.4 (12.0)	55.6 (13.9)	0.007[d]	54.8 (13.7)
Median (Min to Max)	53 (25 to 80)	56 (21 to 90)		
Employment, *n (col %)*				
Disabled	13 (13.8)	29 (7.4)	<0.001[c]	42 (8.6)
Employed	27 (28.7)	153 (39.0)		180 (37.0)
Unemployed	31 (33.0)	82 (20.9)		113 (23.3)
Retired	13 (13.8)	107 (27.3)		120 (24.5)
Other	10 (10.6)	21 (5.4)		31 (6.5)
Cancer Dx, *n (col %)*				
Bone	2(2.1%)	14 (3.6)	0.113[c]	16 (3.3)
Brain/Spine	4(4.3%)	16 (4.1)		20 (4.1)
Breast	14(14.9%)	42 (10.7)		56 (11.5)
Gastrointestinal	12(12.8%)	78 (19.9)		90 (18.5)
Gynecological	10(10.6%)	21 (5.4)		31 (6.4)
Head/Neck	21(22.3%)	50 (12.8)		71 (14.6)
Hematological	9(9.6%)	64 (16.3)		73 (15.0)
Lung	10(10.6%)	45 (11.5)		55 (11.3)
Skin	7(7.4%)	26 (6.6)		33 (6.8)
Urogenital	5(5.3%)	26 (6.6)		31 (6.4)
Other	0(0.0%)	10 (2.6)		10 (2.0)
Years Smoked				
N	85			
Mean (SD)	33.3 (12.2)			
Median (Min to Max)	35 (7 to 54)			
Disease Status, *n (row %)*				
Active	66 (19.9)	265 (80.1)	0.595[c]	331 (68.7)
Stable	27 (17.9)	124 (82.1)		151 (31.3)
Opioid use[e] at Consult				
N	63	279		342
Mean (SD)	127.0 (140.0)	108.2 (143.0)	0.344[d]	111.7 (142.4)
Median (Min to Max)	97.0 (4.2 to 696)	65 (3.8 to 1,525)		70 (3.8 to 1,525)

b. Non-smoker includes former and never smoker

-- percentages may not sum to 100% due to round-off error

[a] Smoker includes cigarette, pipe, and cigars

[c] p-value based on a chi-square test

[d] p-value based on an independent samples t-test

[e] Opioid use is in MEDD mg

Table 2

Differences in Pain and Other Symptoms at First Consult by Smoking Status

	Smoking Status			
	Smoker	**Non-Smoker**	**p-value**	**Total**
Usual Pain Intensity[a]				
N	83	356		439
Mean (SD)	6.2 (2.1)	5.4 (2.2)	0.001[b]	5.5 (2.2)
Median (Min to Max)	6.5 (1 to 10)	5 (0 to 10)	<0.001[c]	5.5 (0 to 10)
Fatigue				
N	90	371		461
Mean (SD)	7.1 (2.7)	6.0 (2.9)	0.002[b]	6.2 (2.9)
Median (Min to Max)	8 (0 to 10)	7.0 (0 to 10)	0.001[c]	7.0 (0 to 10)
Shortness of Breadth				
N	80	370		450
Mean (SD)	3.0 (3.2)	2.6 (2.9)	0.321[b]	2.76 (3.0)
Median (Min to Max)	2.0 (0 to 10)	1.0 (0 to 10)	0.476[c]	1.0 (0 to 10)
Poor Appetite				
N	85	373		458
Mean (SD)	4.6 (3.5)	3.5 (3.4)	0.0008[b]	3.7 (3.4)
Median (Min to Max)	5.0 (0 to 10)	3.0 (0 to 10)	0.016[c]	3.0 (0 to 10)
Depression				
N	85	373		458
Mean (SD)	4.9 (3.5)	3.4 (3.2)	<0.001[b]	3.7 (3.3)
Median (Min to Max)	5 (0 to 10)	3 (0 to 10)	<0.001[c]	3 (0 to 10)
Anxiety				
N	82	371		453
Mean (SD)	5.4 (3.5)	3.8 (3.3)	<0.001[b]	4.1 (3.4)
Median (Min to Max)	6 (0 to 10)	3 (0 to 10)	<0.001[c]	4 (0 to 10)
Drowsiness				
N	81	368		449
Mean (SD)	4.3 (3.0)	4.0 (3.2)	0.374[b]	4.0 (3.1)
Median (Min to Max)	4 (0 to 10)	4 (0 to 10)	0.326[c]	4 (0 to 10)
Difficulty Thinking				
N	81	367		448
Mean (SD)	3.5 (3.3)	3.4 (3.1)	0.808[b]	3.4 (3.1)
Median (Min to Max)	3 (0 to 10)	3 (0 to 10)	0.980[c]	3 (0 to 10)
Insomnia				

	Smoking Status			
	Smoker	**Non-Smoker**	**p-value**	**Total**
N	82	368		450
Mean (SD)	5.1 (3.6)	4.1 (3.4)	0.020[ab]	4.3 (3.5)
Median (Min to Max)	6 (0 to 10)	4 (0 to 10)	0.026[bc]	4 (0 to 10)

[a] Pain was assessed by the BPI usual pain item; all other symptoms were assessed by the ESAS

[b] p-value is based on an independent samples t-test

[c] p-value is based on a Wilcoxon rank sum test

Table 3

Differences in responses on SOAPP-SF items by smoking status

	Outcomes			
	Never	**Infrequently**	**Often**	**p-value**[a]
1. Have mood swings *n (row %)*				
Non-Smokers	109 (27.9)	233 (59.6)	49 (12.5)	0.002
Smokers	17 (18.1)	52 (55.3)	25 (26.6)	
2. Smoke within 1 hour after awakening *n (row%)*				
Smokers only	26 (27.7)	20 (21.3)	48 (51.1)	---
3. Taken meds other than how prescribed *n (row %)*				
Non-Smokers	293 (74.7)	77 (19.6)	22 (5.6)	<0.001
Smokers	49 (52.1)	37 (39.4)	8 (8.5)	
4. Used illegal drugs in the past 5 years *n (row %)*				
Non-Smokers	376 (96.2)	10 (2.6)	5 (1.3)	<0.001
Smokers	76 (80.8)	13 (13.8)	5 (5.3)	
5. Had legal problems or been arrested *n (row %)*				
Non-Smokers	359 (91.6)	32 (8.2)	1 (0.3)	<0.001
Smokers	67 (71.3)	24 (25.5)	3 (3.2)	

[a] p-values are based on a chi-square test

Table 4

Linear multilevel model analyses on changes in pain and opioid use on subsample[a] across visits.

	At Consult	1st Follow-up	6-9 Months
Usual Pain Intensity			
Non-Smokers			
N	356	211	84
Mean (SD)	5.36 (2.23)	4.35 (2.24)	4.01 (1.99)
Smokers			
N	83	59	23
Mean (SD)	6.24 (2.07)	5.02 (2.25)	4.76 (2.52)
LMM Results			
Effect	Est. ± SE	t-value (df)	p-value
Intercept	5.61 ± 0.17	33.2 (190)	<0.001
Smoking Status	0.70 ± 0.30	2.34 (190)	0.02
Visits	−0.95 ± 0.11	−8.46 (263)	<0.001
Opioid Use[b]			
Non-Smokers			
N	279	165	67
Mean (SD)	108.21 (142.96)	114.06 (110.61)	117.79 (122.55)
Smokers			
N	63	48	18
Mean (SD)	127.05 (139.89)	110.00 (110.22)	200.18 (196.36)
LMM Result			
Effect	Est. ± SE	t-value (df)	p-value
Intercept	109.78 ± 11.51	9.54 (190)	<0.001
Smoking Status	17.84 ± 18.91	0.94 (190)	0.35
Visits	9.80 ± 8.19	1.20 (254)	0.23

[a] Subsample descriptives are as follows: For Usual Pain Score (All patients combined) 86 had complete data at all three time points 249 had complete data at time points 1 and 2 90 had complete data at time points 2 and 3 101 had complete data at time points 1 and 3 For Opioid use (All patients combined) 66 had complete data at all three time points 198 had complete data at time points 1 and 2 73had complete data at time points 2 and 3 74had complete data at time points 1 and 3

[b] Opioid use is in MEDD mg. At time of consult, opioid use is based on amount of opioids patients report using on an average day in past week. At subsequent time points, opioid use is based on amount of opioids prescribed.