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The Effects of Depression and Smoking on Pain Severity and Opioid Use in Patients with Chronic Pain

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Abstract

Depression and smoking are common comorbid conditions among adults with chronic pain. The aim of this study was to determine the independent effects of depression on clinical pain and opioid use among patients with chronic pain according to smoking status. A retrospective design was used to assess baseline levels of depression, clinical pain, opioid dose (calculated as morphine equivalents), and smoking status in a consecutive series of patients admitted to a 3-week outpatient pain treatment program from September 2003 through February 2007. Depression was assessed using the Centers for Epidemiologic Studies-Depression scale, and clinical pain was assessed using the pain severity subscale of the Multidimensional Pain Inventory. The study cohort (N = 1241) included 313 current smokers, 294 former smokers, and 634 never smokers. Baseline depression ($P = 0.001$) and clinical pain ($P = 0.001$) were greater among current smokers compared to former and never smokers, and the daily morphine equivalent dose was greater among smokers compared to never smokers ($P = 0.005$). In multivariate linear regression analyses, baseline pain severity was independently associated with greater levels of depression, but not with smoking status. However, status as a current smoker was independently associated with greater opioid use (by 27 mg/day), independent of depression scores. The relationship between depression, smoking status, opioid use, and chronic pain is complex, and both depression and smoking status may be potentially important considerations in the treatment of patients with chronic pain who utilize opioids.

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1. Introduction

Symptoms of depression are common among smokers with chronic pain. In a prospective study that involved adults with chronic pain admitted to a 3-week outpatient pain rehabilitation program, smokers reported significantly greater levels of depression at baseline compared to nonsmokers [30]. Other studies of adults with chronic pain support the observation that levels of depression are consistently greater among smokers compared to nonsmokers [71,72]. In addition to greater levels of depression, smokers with chronic pain also experience greater levels of pain. In a study that utilized a standardized composite measure of pain, smokers presenting to a pain rehabilitation program had significantly greater pain scores compared to former and never smokers [32]. Similarly, elevated levels of pain intensity assessed using a numerical rating scale, have been observed among smokers compared to nonsmokers with chronic pain in some, but not all studies [16,24,71,72]. The frequency of opioid use has been found to be greater among smokers, and these patients consumed significantly greater dosages compared to former and never smokers with chronic pain [31,32].

Increased levels of pain and opioid use in smokers could be due, in part, to the acute effects of nicotine or the consequences of chronic nicotine exposure. Elevated levels of depression could also contribute to increased pain and opioid use in smokers. These links are supported by epidemiologic studies that have identified a reciprocal relationship between depression and the development of chronic pain [10,14,15]. Similarly, experimental pain studies have demonstrated associations between depression and pain [2,17], and patients with depressive symptoms have been reported to be less responsive to opioid analgesia [68,69]. However, the complex relationships between depression, pain, opioid use, and smoking status have not been elucidated. Such knowledge would be important in the development of targeted treatment strategies aimed at addressing these clinical factors.

The primary aim of this study was to determine the association between depression and pain severity according to smoking status in an observational study of a consecutive series of patients with chronic pain admitted to a 3-week pain treatment program. A secondary aim was to determine how depression was associated with opioid use (expressed as morphine equivalent dose) among patients according to smoking status. In two previous studies derived from this cohort of patients, the relationships between pain, smoking and opioid tapering were examined [32], and sex differences in treatment outcomes of smokers with chronic pain were described [31]. The current study is unique, and distinguished from these two previous manuscripts in that smoking status and depression were considered simultaneously while examining their associations with pain severity and opioid use.

2. METHODS

2.1. Participants

This study was approved by the Mayo Foundation Institutional Review Board. All adults consecutively admitted to the Mayo Comprehensive Pain Rehabilitation Center from September 2003 through February 2007 were eligible for study inclusion. Over this period of time, 1257 individuals with chronic pain were admitted. Data were collected prospectively as an integral part of the pain treatment program. Prior to admission, these patients provided authorization for the use of their medical records for research purposes. Patients who used forms of tobacco other than cigarettes were excluded from the study; 7 patients used oral tobacco, 5 smoked cigars or a pipe, and 1 patient used multiple forms of tobacco. The form of tobacco use could not be ascertained for 3 patients. Thus, the study cohort included 1241 participants (928 women and 313 men).

2.2. Study setting

The current report represents a secondary analysis of this dataset, portions of which have been previously published [31,32]. To briefly summarize the clinical setting, a cognitive behavioral model serves as the basis for treatment, and the primary treatment goal of the outpatient program is restoration of physical and emotional functioning [8,65]. Prior to admission, patients were receiving medical care from a physician and experienced incomplete symptomatic relief from multiple pharmacologic trials, repeated courses of physical therapy or interventional pain procedures.

2.3. Smoking status

Smoking status was assessed upon admission to the pain treatment center using a self-report questionnaire as previously described [31,32]. All patients were asked to "describe your history of smoking cigarettes." Patients could identify themselves as "never smokers," "former smokers" who have not smoked for one month, or "current smokers."

2.4. Determination of morphine equivalent dose

At admission, the daily opioid dose of each patient was determined by self-report and review of pharmacy records, as previously described [13,66]. The daily opioid dose was converted to daily morphine equivalents using an equianalgesic conversion software program [21] that has been used extensively at our outpatient treatment center [13,31,32,66].

2.5. Measures

2.5.1. Demographics and clinical characteristics—Baseline demographic and clinical characteristics were collected at admission including age, pain duration, primary pain site, marital status, years of education, and medication use.

2.5.2. Depression—The Center for Epidemiologic Studies-Depression scale (CES-D) provides a measure of depressive symptoms that have occurred in the past week. Four factors comprise the composite CES-D score including measures of general depressive and somatic symptoms, positive affect, and interpersonal difficulties. The self-administered questionnaire has established reliability and validity among adults with chronic pain [26,73]. The CES-D is scored on a 4-point Likert scale, and total scores range from 0 to 60 where higher scores indicate greater levels of depression. This measure of depressive symptoms has been used extensively at our pain treatment center [12,30,31,34,66].

2.5.3. Pain Severity—Pain severity was assessed on the day of admission using the pain severity subscale of the Multidimensional Pain Inventory (MPI) [38]. This self-report questionnaire has proven reliability and construct validity [3]. The pain severity subscale is a composite measure of clinical pain, and is calculated from the responses to the following three questions: 1) "Rate the level of your pain at the present moment;" 2) "On the average, how severe has your pain been during the last week;" and 3) "How much suffering do you experience because of your pain." Responses to each question are scored on a 7-point Likert scale where 0 indicates no pain or suffering, and 6 indicates extreme pain or suffering. Raw scores from the pain severity subscale were converted to standardized *T*-scores using the means and standard deviations from a heterogeneous group of over 700 patients with chronic pain [55]. The standardized subscale has a mean of 50 (range 0 to 100) and a standard deviation of 10, where higher scores indicate greater pain severity. This standardized measure of clinical pain has been used extensively to assess the outcomes of patients admitted to our pain treatment program [12,31,32,33,34,54,66].

2.6. Data Analyses

Demographics (age, sex, ethnicity, marital status, educational status, employment status) and clinical characteristics (pain duration, primary pain site, depression, pain severity, frequency of opioid use, daily morphine equivalent dose) of current, former, and never smokers were described. Mean and standard deviation (SD) were reported for continuous variables, and count and proportion were reported for categorical variables. Comparison among current, former and never smokers were made using univariate analysis of variance (ANOVA) for continuous variables and chi-square test for categorical variables. Post-hoc contrast analyses were conducted using Tukey HSD to assess pairwise comparisons when significant group differences were observed.

Linear regression analyses were performed with MPI pain severity at baseline as the outcome variable. Univariate regressions were first performed on smoking status and CES-D scores, respectively. Both smoking status and CES-D scores were then entered in a model to test potential mediation or confounding effects between the two predictors. Interaction effect between smoking and CES-D was assessed by entering an interaction term (which was the product of the two factors) in the regression as a new variable. The final model contained both smoking status and CES-D scores as predicators, controlling for age, sex, marital status, education, employment status, pain duration, and opioid use.

Linear regression analyses were used with baseline morphine equivalent dose as the outcome variable. Univariate regressions were first performed separately on smoking status and CES-D scores. The final model contained both smoking status and CES-D score as predictors, and adjusted for age, sex, marital status, education, employment status, pain duration, and baseline MPI pain severity.

The level of significance for all statistical tests was set at $P < 0.05$, and all analyses were completed using Stata, version 10.0 (College Station, TX).

3. Results

3.1. Sample characteristics

The study cohort (N = 1241) included 313 men and 928 women of whom 313 were current smokers, 294 were former smokers and 634 were never smokers (Table 1). Females were more likely to be never smokers, and current smokers were younger than former and never smokers. Pain duration was longer among former smokers compared to current and never smokers, consistent with the higher age of former smokers. Current smokers were more likely to be single or divorced, and had fewer years of education compared to former and never smokers. At this baseline point (pretreatment), the prevalence of daily opioid use was higher among current smokers and former smokers compared to never smokers. The morphine equivalent dose was greater among current smokers compared to never smokers, but no significant differences were observed between former smokers compared to current or never smokers. Current smokers had higher CES-D and pain severity scores compared to former and never smokers (Table 2).

3.2. Associations between pain severity, depression and smoking status

In univariate linear regression with baseline pain severity as the dependent variable (Table 3), the coefficient for current smoking was significant, where the mean pain score for current smokers was 2.89 points higher than never smokers. Univariate linear regression on the CES-D scores showed that each 1 point increase in the CES-D score was associated with a 0.28 point increase in pain severity ($P < 0.001$). When both smoking status and CES-D score were included in a model without adjusting for other factors, the coefficient for current

smoking was still significant but reduced to 1.47 (P=0.022), suggesting that a portion of the effect of current smoking on pain severity was explained by depression. There was no significant interaction (P=0.874, given by the test for interaction terms in the regression model) between smoking status and depression on pain severity in that the magnitude of the increase in pain severity associated with increases in the CES-D did not depend on smoking status. Thus, no interaction term was included in the final regression model.

In the final multiple linear regression model with baseline MPI pain severity as the dependent variable that included age, sex, marital status, education, employment status, pain duration, and daily morphine equivalent dose, the coefficient for smoking was no longer significant (Table 3), indicating that baseline pain severity was not independently associated with smoking status. However, the coefficient for CES-D in the final model was statistically significant, suggesting that the effect of smoking on pain severity could be explained by an association of smoking status with depression and other factors (Table 3). In this model, other factors that were significantly associated with greater pain severity included older age, less education, unemployment, and greater opioid use.

3.3. Associations between morphine equivalent dose, depression and smoking status

In univariate regression with baseline morphine equivalent dose as the dependent variable (Table 4), status as a current smoker and higher CES-D scores were associated with greater morphine equivalent dosages at baseline. After pain severity was included in the multiple regression model, depression was no longer significantly associated with baseline morphine equivalent dose. However, after adjusting for other factors in the final multiple linear regression model, current smoking was independently associated with a 27 mg/day increase in morphine equivalent dose compared to never smokers (Table 4). Other factors significantly associated with greater morphine equivalent dose in this model included male sex, being unemployed, and having greater pain severity.

4. Discussion

The main finding of this study was that in patients presenting to a pain rehabilitation program, baseline pain severity was independently associated with greater levels of depression but not smoking status. However, status as a current smoker was associated with use of greater morphine equivalent dosages independent of depression scores, which substantiates previous observations that nicotine may have a direct effect on opioid consumption.

Previous studies have found various associations between depression, pain and smoking status. The association between depression and pain severity observed herein is supported by epidemiologic and other experimental studies that have demonstrated depression is associated with painful physical symptoms, including spinal pain and other chronic pain conditions [14,15,49,64]. Painful symptoms may also contribute to worse treatment outcomes of depression [18,41]. There is also a strong association between depression and smoking [28,39], and the co-occurrence of these two conditions have been well documented [6,19]. Indeed, recent data suggests that up to 45% of adults with depressive disorders smoke [40]. Numerous epidemiologic studies have identified an association between smoking and chronic pain. For instance, prospective studies showed that smoking during adolescence was associated with development of chronic pain, and was predictive of lumbar spine surgery during adulthood [42,43,45]. In several longitudinal studies that ranged in duration from 8 to greater than 15 years, smoking was associated with development of chronic pain, incidental sciatic pain and hospitalization for intervertebral disc disorders [29,36,46].

The mechanisms responsible for the associations between depression, pain, and smoking are not clear. Functional imaging studies demonstrate that discrete brain regions are responsible for modulating pain in response to negative affect in subjects with and without mood disorders [23,27,58]. Functional imaging studies also suggest that depression and smoking may share common neurobiological pathways [7,9], and similar genetic, environmental and other shared mental health factors may contribute to the risk of developing both conditions [44,47,50,52]. The interactions between smoking, depression and pain could also be influenced by nicotine withdrawal, which could occur insidiously during time intervals between active periods of smoking. In both human [48,51,53] and animal [1,56] studies, nicotine deprivation has been associated with development of acute withdrawal hyperalgesia, which has led some investigators to suggest that rapid dissipation of the systemic effects of nicotine could contribute to pain-related symptoms during periods of relative nicotine deprivation. Nicotine withdrawal has also been associated with depressive symptoms [35,37,74], but the potential effects of transient depressive symptoms on measures of clinical pain have not been previously studied. Depression, in turn, may sustain smoking behavior, and smokers with depression may smoke to elevate mood [25]. In addition, pain has been suggested to be a motivator to smoke [20]. Although many prior studies have analyzed pairwise associations between depression, pain, and smoking status, few have simultaneously considered the potential interactions between all three. Our results reveal that the association between smoking status and pain severity in this selected population was largely explained by increased levels of depression in smokers rather than an effect of smoking status on pain. This finding is consistent with our recent analysis of a national representative longitudinal data, which showed that depression was a significant predictor of the incidence of pain, and smoking only increased the likelihood of pain onset in those who were depressed [60].

The second main observation from this study was that the association between smoking status and increased opioid consumption was independent of depression scores, which is in contrast to the analyses of pain severity. This result implies that a direct interaction exists between nicotinic and opioid pharmacology. In animal models, the antinociceptive effects of nicotine are mediated, in part, by the endogenous opioid system [56,61], and morphine antinociception is enhanced in a dose-dependent manner by stimulation of supraspinal nicotinic acetylcholine receptors [4,5,61,63]. In humans, there is a clear dose response relationship between nicotine and opioid consumption in adults receiving maintenance methadone therapy for opiate addiction, as increases in methadone consumption are associated with increases in cigarette smoking [11,57]. Conversely, increases in nicotine consumption have been associated with increases in the self-administration of methadone [62]. The association between nicotine and opioid consumption is supported by a functional imaging study wherein significant activation of mu-opioid receptor neurotransmission was observed in adult smokers following repletion of nicotine deprivation [59]. Thus, the observations from this study, and the findings of other preclinical and clinical investigations, support the supposition that the increased consumption of opioids by smokers could be related, in part, to a direct but incompletely understood interaction between nicotinic and opioid pharmacology.

These results have several potential clinical implications in the care of patients with chronic pain. First, smoking may be an important indicator of comorbid depression among patients with chronic pain, and these individuals should be carefully screened for depressive disorders. Second, depression may contribute to the development of painful symptoms, which should be addressed in the treatment of symptoms that may not be directly attributed to the primary chronic pain condition. Third, smokers may be at risk of opioid dose escalation, which should be considered in the risk stratification of patients prior to initiating long-term opioid therapy. Finally, given the observation that nicotine may have analgesic

effects, although the findings from human studies are mixed, patients and clinicians may be concerned that quitting smoking may worsen pain symptoms. Although there are no direct studies regarding how quitting smoking may affect chronic pain, the lack of an independent association between smoking and pain severity suggests that smoking cessation may not adversely impact pain symptoms. However, our results only suggest this hypothesis, which remains to be tested.

This study has several limitations. First, smoking status was assessed based on patient self-report and was not biochemically confirmed. Second, the study population was highly selected and may not represent the general population of patients with chronic pain who smoke. However, the demographic characteristics of our cohort were similar to the characteristics of a random sample of community dwelling adults with chronic pain derived from the catachment area of our pain treatment program [70]. Furthermore, the smoking characteristics of patients who participated in a previously reported prospective study conducted at our pain treatment center [30] were comparable to other groups of smokers [22,24,67]. Third, other confounding variables, including body mass index, the number of cigarettes smoked daily, and the use of concurrent medications that could have affected opioid metabolism, were not available for the cohort but these factors could have influenced our analyses. Finally, this study represents an analysis of cross-sectional data; therefore, the study design limits any causal inferences on the relationship between smoking, depression and chronic pain.

In conclusion, the relationship between depression, smoking status, opioid use, and chronic pain is complex. In this study population, status as a smoker was associated with greater opioid use, but not greater pain severity. The results suggest that both depression and smoking status are potentially important considerations in the treatment of patients with chronic pain.

Summary

This study found that pain severity was associated with greater depression but not smoking; however, smoking was associated with greater opioid use, independent of depression.

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Table 1

Baseline demographic and clinical characteristics of smokers, former smokers and never smokers.

Characteristic	Current Smoker (n = 313)	Former Smoker (n = 294)	Never Smoker (n = 634)	*P* Value*
Age (*mean* ± *SD*)	42.8 ± 11.1[a]**	50.9 ± 13.2[b]	46.2 ± 14.5[c]	<0.001
Sex (*N*, %)				0.002
Male	88 (28)	91 (31)	134 (21)	
Female	225 (72)	203 (69)	500 (79)	
Ethnicity				0.431
Caucasian	301 (96)	286 (97)	592 (93)	
Hispanic	3 (1)	5 (2)	18 (3)	
African American	7 (2)	2 (1)	13 (2)	
Other	2 (1)	1 (0)	11 (2)	
Marital status				<0.001
Married	152 (49)	214 (73)	435 (69)	
Single/Divorced	161 (51)	80 (27)	199 (31)	
Years of education	13.5 ± 2.5[a]	14.6 ±2.8[b]	14.8 ±2.8[b]	<0.001
Currently employed	77 (25)	76 (26)	196 (32)	0.142
Pain duration, years	8.6 ± 9.3[a]	12.0 ± 11.8[b]	9.6 ± 10.9[a]	0.001
Primary pain site				0.649
Low back	98 (31)	78 (27)	156 (25)	
Fibromyalgia	56 (18)	70 (24)	131 (21)	
Headache	24 (8)	25 (9)	69 (11)	
Generalized	27 (9)	23 (8)	53 (8)	
Abdominal	22 (7)	18 (6)	31 (5)	
Neck	20 (6)	18 (6)	39 (6)	
Upper extremity	11 (3)	5 (2)	17 (3)	
Lower extremity	10 (3)	12 (4)	20 (3)	
Pelvic	9 (3)	6 (2)	27 (4)	
Facial	2 (1)	3 (1)	9 (1)	
Chest wall	4 (1)	3 (1)	13 (2)	
Other	30 (10)	33 (11)	69 (11)	
Opioid use	168 (54)	164 (56)	290 (46)	0.006
Morphine equivalent dose (mg/day)	78.9 ± 151.6[a]	61.0 ± 116.6[ab]	48.4 ± 104.4[b]	0.005

* Univariate analysis of variance (ANOVA) for continuous variables, chi-square for categorical variables.

** Different superscripts denote Tukey HSD post-hoc statistical significance ($P < 0.05$) between groups, and similar superscripts denote no statistical significance.

Table 2

Baseline scores of the Centers for Epidemiologic Studies-Depression scale and Multidimensional Pain Inventory pain severity subscale based on smoking status.

Variable	Current Smoker (N = 313)	Former Smoker (N = 294)	Never Smoker (N = 634)	*P* Value*
CES-D				
Baseline	30.2 ± 12.5[a]**	26.1 ± 11.9[b]	25.0 ± 12.2[b]	<0.001
MPI Pain Severity				
Baseline	49.8 ± 9.8[a]	47.8 ± 9.0[b]	46.9 ±9.4[b]	<0.001

* Univariate analysis of variance (ANOVA).

** Mean ± standard deviation; different superscripts denote Tukey HSD post-hoc statistical significance ($P < 0.05$) between groups and similar superscripts denote no statistical significance.

Table 3

Linear regression analyses with baseline MPI pain severity as the outcome variable.

	Beta coefficient in univariate analysis (95% CI)	P	Beta coefficient in multivariate analysis* (95% CI)	P
Smoking status				
Never	0.00		0.00	
Former	0.86 (−0.45, 2.18)	0.197	−0.06 (−1.29, 1.17)	0.922
Current	2.89 (1.58, 4.20)	<0.001	0.51 (−0.76, 1.78)	0.427
CES-D score	0.28 (0.23, 0.31)	<0.001	0.25 (0.21, 0.29)	<0.001
Age	0.03 (−0.01, 0.07)	0.130	0.06 (0.02, 0.10)	0.002
Female sex	−0.45 (−1.70, 0.79)	0.474	−0.41 (−1.56, 0.74)	0.485
Married	−0.74 (−1.87, 0.39)	0.201	−0.83 (−1.92, 0.26)	0.137
Years of education	−0.69 (−0.89, −0.50)	<0.001	−0.53 (−0.71, −0.34)	<0.001
Currently employed	−4.45 (−5.62, −3.29)	<0.001	−2.72 (−3.84, −1.60)	<0.001
Pain duration	0.00 (−0.05, 0.05)	0.991	−0.01 (−0.06, 0.04)	0.627
Morphine equivalent dose (per 50 mg/day)	0.45 (0.23, 0.67)	<0.001	0.28 (0.07, 0.49)	0.008

*Adjusted for all other factors listed in the table.

Table 4

Linear regression analyses with baseline morphine equivalent dose as the outcome variable.

	Beta coefficient in Univariate analysis (95% CI)	P	Beta coefficient in multivariate analysis* (95% CI)	P
Smoking status				
Never	0.00		0.00	
Former	12.54 (−4.17, 29.26)	0.141	10.39 (−6.74, 27.51)	0.234
Current	30.44 (14.07, 46.81)	<0.001	26.77 (9.11, 44.44)	0.003
CES-D score	0.89 (0.34, 1.44)	<0.001	0.38 (−0.23, 0.98)	0.219
Age	−0.31 (−0.81, 0.18)	0.211	−0.45 (−1.02, 0.11)	0.115
Female sex	−34.31 (−49.76, −18.87)	<0.001	−32.99 (−48.96, −17.01)	<0.001
Married	2.96 (−11.17, 17.08,)	0.682	6.41 (−8.84, 21.66)	0.410
Years of education	−0.35 (−2.81, 2.12)	0.782	1.84 (−0.73, 4.42)	0.160
Currently employed	−23.42 (−38.45, −8.39)	0.002	−19.97 (−35.70, −4.24)	0.013
Pain duration	0.03 (−0.60, 0.67)	0.919	0.13 (−0.54, 0.79)	0.707
MPI pain severity	1.45 (0.74, 2.17)	<0.001	1.09 (0.29, 1.90)	0.008

*Adjusted for all other factors listed in the table.