

The Association of Current Tobacco Status With Pain and Symptom Severity in Fibromyalgia Patients

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Abstract

Objective: To describe current tobacco use among patients with newly confirmed fibromyalgia and evaluate the association between tobacco use status and severity of reported pain and other fibromyalgia symptoms.

Patients and Methods: Participants in this study were adult patients (N=1068) with fibromyalgia who met American College of Rheumatology 2010/2011 clinical criteria for fibromyalgia at the time of initial presentation to a Midwest fibromyalgia clinic (June 1, 2018, through May 31, 2019). Multiple linear regression analyses were performed to assess the association of tobacco use status with the Widespread Pain Index (WPI) and Symptom Severity Scale (SSS) scores. Covariates included in these analyses included age, sex, body mass index, depression, opioid medication use, and use of fibromyalgia-specific pharmacotherapy.

Results: The patients were largely women (87.0%; n=929), white (87.9%; n=939), and with an average \pm SD age of 46.6 ± 13.9 years. The WPI and SSS scores were significantly greater in current tobacco users compared with never tobacco users (WPI effect estimate [EE] = 1.03; 95% CI, 0.30 to 1.76; type III $P=.020$; SSS EE = 0.47; 95% CI, 0.11 to 0.84; type III $P=.036$). The WPI score was negatively associated with age (EE = -0.02 per year; 95% CI, -0.03 to -0.001 per year; $P=.037$) and no use of opioid medication (EE = -1.08 ; 95% CI, -1.59 to -0.57 ; $P<.001$) while positively associated with higher body mass index (EE = 0.03 per 1 kg/m^2 ; 95% CI, 0.001 to 0.06 per kg/m^2 ; $P=.04$) and higher Patient Health Questionnaire-9 score (EE = 0.12 ; 95% CI, 0.08 to 0.16 ; $P<.001$).

Conclusion: The results of our study suggest that tobacco use is associated with greater pain and other symptom severity in patients with fibromyalgia. These findings have important clinical and research implications for patients with fibromyalgia who use tobacco and who may benefit from early identification and timely implementation of tobacco cessation treatment to decrease pain and improve overall quality of life.

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Tobacco use has been acknowledged as the most preventable cause of death in the United States.^{1,2} Despite coordinated efforts and nationwide campaigns to reduce tobacco use, it has not been eliminated. The rate of tobacco use (ie, cigarettes, cigars, pipe tobacco, and smokeless tobacco) has been reduced over time by approximately 43% (from 45.3% to 25.8%) among adults 18 to 25 years of age and reduced 29.0% among adults 26 years or older (from 29.9% to 23.4%)³ but more needs to be done. Tobacco use is causally

linked to cancer, cardiovascular diseases, chronic lung disease, and more, resulting in an economic cost of more than \$170 billion in medical care each year.⁴

Among the US adult population, high rates of cigarette use are reported in people with current or lifetime chronic neck or back pain (35%). This is nearly 3 times greater than the current national prevalence.⁵ The reasons for the observed association between smoking and chronic pain^{6,7} remain unclear. Suggested mechanisms include pain receptor sensitization

whereby smokers perceive even the smallest amount of pain as being severe⁸ or an unexplained direct biological impact of nicotine on central pain perception.^{5,9}

In addition to its highly addictive properties, data derived from preclinical studies indicate that nicotine may exhibit analgesic properties through the indirect activation of nicotinic acetylcholine receptors (specifically $\alpha 4\beta 2$, $\alpha 3$, and $\alpha 7$),⁸ leading us to postulate that smoking may be used by individuals with chronic pain as a way to ease/lessen the pain.⁸ However, although smoking in the short term may induce analgesia for some patients with chronic pain, empirical evidence from the past decade has established a complex reciprocal relationship between smoking (ie, tobacco) and chronic pain, with several plausible mechanisms.⁵ There is mounting scientific evidence confirming associations between chronic pain and tobacco use. These include associations between chronic pain and greater nicotine dependence, perceived barriers to and more difficulty quitting, and other cessation-related problems.¹⁰⁻¹²

In addition, smoking has been associated with an increased adverse effect in response to pain,¹³ increased pain-related occupational disability,¹⁴ and an increase in pain intensity.¹² The association between smoking and increased pain intensity has primarily been observed in studies in the general patient population reporting chronic pain.⁷

Fibromyalgia is estimated to occur in approximately 2% to 8% of the population and is characterized by widespread pain, fatigue, cognitive difficulties, and sleep disturbances.^{15,16} In addition, patients with fibromyalgia have a high level of medical and psychiatric comorbid conditions, including myocardial infarction, hypertension, diabetes, anxiety, depression, and post-traumatic stress disorder.^{16,17} Goesling et al⁹ estimated the smoking rate among patients with fibromyalgia at 38.7% compared with 24.7% among patients without fibromyalgia. In their study of 1566 patients who reported to an outpatient pain clinic for a range of conditions, current smoking was significantly associated with both pain severity and functional impairment in patients with fibromyalgia.⁹

We hypothesize that among our patients with newly confirmed fibromyalgia, pain and symptom severity would be distributed along a spectrum, with the most severe pain and

symptom scores occurring in current tobacco users, followed by former tobacco users (depending on how recently they quit tobacco use) and with the lowest scores occurring in never tobacco users. Although previous work has been undertaken within our institution describing the relationship between fibromyalgia and smoking, none to date have reviewed the relationship between overall tobacco use (cigarettes, cigars, pipes, and chewing tobacco), status of use (current, past, and never), pain severity, and fibromyalgia.

The purpose of the present study was to describe the tobacco use status of patients with newly confirmed fibromyalgia and evaluate the association between tobacco use status and severity of reported pain and other fibromyalgia symptoms.

PATIENTS AND METHODS

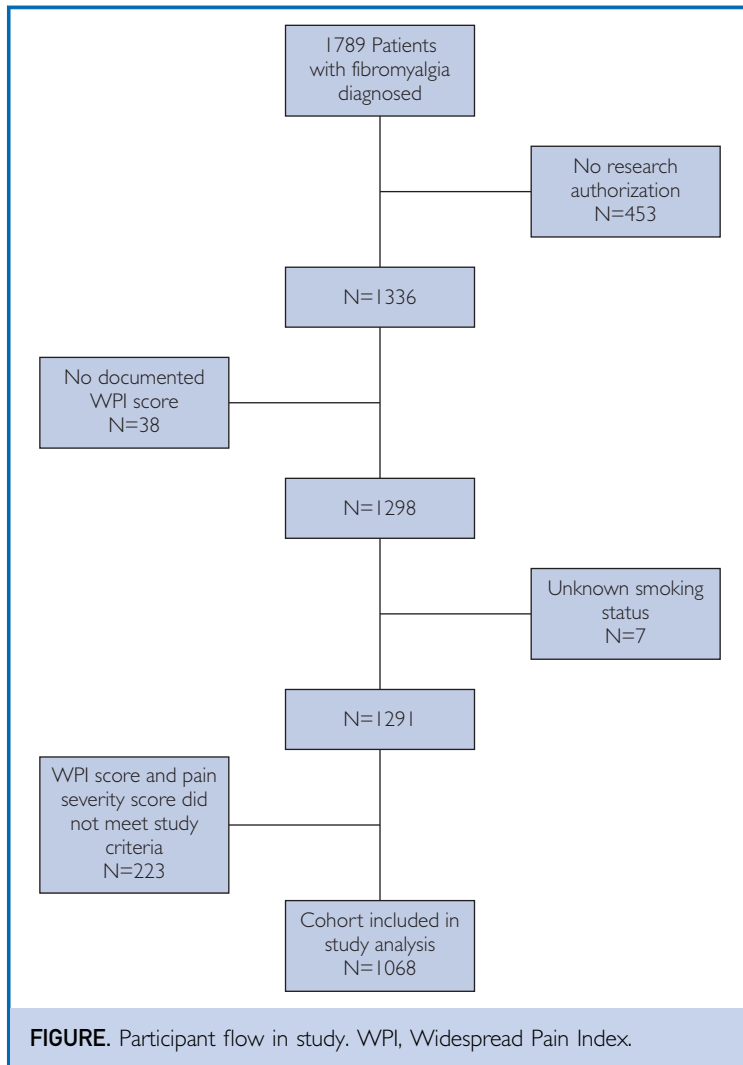
This retrospective study was reviewed by Mayo Clinic Institutional Review Board and determined to be exempt under section 45 CFR 46.101, item 2. During the study, all significant changes to study design and procedures were appropriately filed, reviewed, and approved by the Institutional Review Board.

Study Population

We reviewed the electronic medical records (EMRs) of 1789 patients with fibromyalgia, 18 years or older, who presented at our institution's fibromyalgia clinic between June 1, 2018, and May 31, 2019. A total of 721 patients did not meet study criteria and were excluded from the study analysis (Figure). Patients were excluded if they had missing tobacco status, declined Minnesota research authorization, or did not currently meet fibromyalgia diagnostic criteria. Patients were classified as having newly confirmed fibromyalgia if they met the fibromyalgia clinical diagnostic criteria (ie, if their Widespread Pain Index [WPI] score was ≥ 7 and their Symptom Severity Scale [SSS] score was ≥ 5 or they had a WPI score between 3 and 6 with an SSS score ≥ 9).¹⁸ Tobacco use status was determined from the EMR. The current analysis is based on data from the 1068 patients who met inclusion criteria.

Data Collection

Patient demographics, tobacco status, fibromyalgia pharmacotherapy, and pain scores at



the time of diagnosis were abstracted from the EMRs for the study population. Tobacco status was classified as current tobacco user (used tobacco at time of diagnosis), former tobacco user (defined as not having used tobacco in the 6 months before diagnosis), and never used any tobacco (self-reported as never using any tobacco in their lifetime).¹⁹ Fibromyalgia-specific pharmacotherapy indicates use of US Food and Drug Administration–approved medications for fibromyalgia, including duloxetine, milnacipram, pregabalin, and other medications such as gabapentin, tricyclics, and low-dose naltrexone that are supported by evidence.²⁰ Opioid medications that were used to indicate the binary opioid use variable were hydrocodone, oxycodone, tramadol,

morphine, fentanyl, oxycodone, buprenorphine, and hydromorphone. The WPI is a measure used clinically in the fibromyalgia clinic to define and collect data on pain in 4 quadrants plus axial pain, and the SSS assesses fatigue, unrefreshing sleep, brain fog, headache, abdominal pain, and depression.²¹

Data Analyses

Baseline patient characteristics are summarized using mean \pm SD, median, and range for continuous variables and frequency count and percentage for categorical variables. These characteristics were compared across the 3 tobacco use groups (former, never, and current) by using the Kruskal-Wallis test for continuous variables and χ^2 test for categorical variables. The 2 pain variables evaluated were the WPI and the SSS. These variables were modeled separately using multivariable linear regression. For these analyses, the primary explanatory variable of interest was tobacco use status (current vs former vs never) and covariates were included for age, body mass index (BMI; calculated as the weight in kilograms divided by the height in meters squared), sex, and use of fibromyalgia pharmacotherapy. Depression was also examined as an explanatory variable using the Patient Health Questionnaire-9 (PHQ-9) scale as a covariate in the WPI model. The PHQ-9 was used as a proxy measure for depression, which in turn has been linked with fibromyalgia.^{11,22} Results from the multiple linear regression analyses are summarized by presenting the estimated regression coefficients with 95% CIs. In all cases, $P < .05$ was considered significant. SAS statistical software (version 9.4; SAS Institute Inc) was used for all analyses.

RESULTS

Most patients in the study were women (87%; $n=929$), were white (88%; $n=939$), and with a mean \pm SD age of 46.6 ± 13.9 years. Additional patient characteristics are reported in Table 1. As expected, age, sex, and BMI differed across tobacco status groups, with current tobacco use having the youngest mean age, lowest mean BMI, and highest percentage of men. Concomitant medication use was similar across tobacco use groups. The average \pm SD WPI score for each tobacco user group was 13.2 ± 3.6 for current users, 12.4 ± 3.8 for former users, and

TABLE 1. Descriptive Characteristics

	Tobacco Status			Total (N=1068)	P
	Current (n=130)	Former (n=238)	Never (n=700)		
Age (y)					.0001 ^a
Mean ± SD	43.1±10.79	49.2±12.64	46.4±14.69	46.6±13.93	
Median	42.0	49.0	47.5	47.0	
Range	19.0-70.0	18.0-84.0	18.0-82.0	18.0-84.0	
Body mass index (kg/m ²)					.0071 ^a
Mean ± SD	29.8±7.60	32.0±8.40	30.1±7.86	30.5±7.99	
Median	28.2	30.4	29.2	29.4	
Range	16.9-57.1	17.8-62.7	14.5-65.3	14.5-65.3	
Missing	5	16	30	51	
Sex, no. (%)					<.0001 ^b
Female	101 (77.7)	196 (82.4)	632 (90.3)	929 (87.0)	
Male	29 (22.3)	42 (17.6)	68 (9.7)	139 (13.0)	
Race, no. (%)					.9080 ^b
Asian	2 (1.5)	2 (0.8)	14 (2.0)	18 (1.7)	
Black	1 (0.8)	2 (0.8)	15 (2.1)	18 (1.7)	
American Indian/Alaskan Native	2 (1.5)	2 (0.8)	8 (1.1)	12 (1.1)	
Other	3 (2.3)	5 (2.1)	17 (2.4)	25 (2.3)	
Unknown	6 (4.6)	13 (5.5)	37 (5.3)	56 (5.2)	
White	116 (89.2)	214 (89.9)	609 (87.0)	939 (87.9)	
Tobacco use, no. (%)					
All tobacco use	130	238	0	368	
No tobacco use	0	0	700	700	
Smoking only ^c	116 (89.2)	219 (92.0)	0 (0.0)	335 (31.3)	
Chewing only	5 (3.8)	8 (3.4)	0 (0.0)	13 (1.2)	
Both	9 (6.9) ^d	11 (4.6)	0 (0.0)	20 (1.9)	
Duloxetine, no. (%)					.2908 ^a
No	92 (70.8)	178 (74.8)	539 (77.0)	809 (75.7)	
Yes	38 (29.2)	60 (25.2)	161 (23.0)	259 (24.3)	
Milnacipran, no. (%)					.1004 ^a
No	126 (96.9)	237 (99.6)	691 (98.7)	1054 (98.7)	
Yes	4 (3.1)	1 (0.4)	9 (1.3)	14 (1.3)	
Pregabalin, no. (%)					.6390 ^a
No	117 (90.0)	217 (91.2)	646 (92.3)	980 (91.8)	
Yes	13 (10.0)	21 (8.8)	54 (7.7)	88 (8.2)	
Gabapentin, no. (%)					.1256 ^a
No	87 (66.9)	170 (71.4)	525 (75.0)	782 (73.2)	
Yes	43 (33.1)	68 (28.6)	175 (25.0)	286 (26.8)	
Amitriptyline/nortriptyline, no. (%)					.9730 ^a
No	113 (86.9)	206 (86.6)	610 (87.1)	929 (87.0)	
Yes	17 (13.1)	32 (13.4)	90 (12.9)	139 (13.0)	
Naltrexone, no. (%)					.5764 ^b
No	129 (99.2)	233 (97.9)	685 (97.9)	1047 (98.0)	
Yes	1 (0.8)	5 (2.1)	15 (2.1)	21 (2.0)	
Any fibromyalgia medication, no. (%) ^e					.3734 ^b
None	55 (42.3)	110 (46.2)	341 (48.7)	506 (47.4)	
Any	75 (57.7)	128 (53.8)	359 (51.3)	562 (52.6)	
Hydrocodone, no. (%)					.6168 ^b
No	113 (86.9)	209 (87.8)	626 (89.4)	948 (88.8)	
Yes	17 (13.1)	29 (12.2)	74 (10.6)	120 (11.2)	

Continued on next page

TABLE 1. Continued

	Tobacco Status				P
	Current (n=130)	Former (n=238)	Never (n=700)	Total (N=1068)	
Oxycodone, no. (%)					.1229 ^b
No	108 (83.1)	205 (86.1)	623 (89.0)	936 (87.6)	
Yes	22 (16.9)	33 (13.9)	77 (11.0)	132 (12.4)	
Tramadol, no. (%)					.4212 ^b
No	115 (88.5)	209 (87.8)	596 (85.1)	920 (86.1)	
Yes	15 (11.5)	29 (12.2)	104 (14.9)	148 (13.9)	
Morphine, no. (%)					.0497 ^b
No	127 (97.7)	234 (98.3)	697 (99.6)	1058 (99.1)	
Yes	3 (2.3)	4 (1.7)	3 (0.4)	10 (0.9)	
Fentanyl, no. (%)					.3641 ^b
No	130 (100)	236 (99.2)	698 (99.7)	1064 (99.6)	
Yes	0 (0.0)	2 (0.8)	2 (0.3)	4 (0.4)	
Oxymorphone, no. (%)					.0270 ^b
No	129 (99.2)	238 (100)	700 (100)	1067 (99.9)	
Yes	1 (0.8)	0 (0.0)	0 (0.0)	1 (0.1)	
Buprenorphine, no. (%)					.3932 ^b
No	128 (98.5)	235 (98.7)	696 (99.4)	1059 (99.2)	
Yes	2 (1.5)	3 (1.3)	4 (0.6)	9 (0.8)	
Hydromorphone, no. (%)					.5317 ^b
No	128 (98.5)	237 (99.6)	694 (99.1)	1059 (99.2)	
Yes	2 (1.5)	1 (0.4)	6 (0.9)	9 (0.8)	
Any opioid medication, ^c no. (%)					.0701 ^b
None	83 (63.8)	156 (65.5)	502 (71.7)	741 (69.4)	
Any	47 (36.2)	82 (34.5)	198 (28.3)	327 (30.6)	

^aKruskal-Wallis P value.^bChi-squared P value.^cCigarettes, cigars, or pipes.^dThree people formally chewed tobacco.^eMedications were pulled from any prescriptions during the time frame of 1 year before the patient's fibromyalgia clinic visit.

12.0±3.9 for those who have never used. The average ± SD SSS scores were 9.5±1.9 for current users, 9.0±1.8 for former users, and 8.9±1.9 for never users.

Results from the multivariable linear regression model with WPI score as the outcome are reported in Table 2. The WPI scores differed significantly ($P=.020$) across tobacco status categories, with current tobacco users having higher WPI scores compared with never tobacco users (effect estimate [EE] = 1.03; 95% CI, 0.30 to 1.76). The WPI scores were also found to decrease with age (EE = -0.02 per year; 95% CI, -0.04 to -0.01 per year; $P=.004$), increase with BMI (EE = 0.04 per kg/m²; 95% CI, 0.01 to 0.07 per kg/m²; $P=.014$), and was lower for those not taking fibromyalgia-specific pharmacotherapy (EE = -0.48; 95% CI, -0.95 to -0.01; $P=.048$) and lower for those not

taking opioid medications (EE = -1.16; 95% CI, -1.68 to -0.64; $P<.001$).

Table 3 shows the results of the model for the outcome of the multivariable analysis of the SSS score. The SSS scores differed significantly ($P=.036$) across tobacco status categories, with current tobacco users having higher symptom severity compared with never tobacco users (EE = 0.47; 95% CI, 0.11 to 0.84) and scores were also found to decrease with age (EE = -0.02 per year; 95% CI, -0.02 to -0.01 per year; $P<.001$).

When the PHQ-9 score was included in the WPI model (Table 4), WPI scores significantly increased with increased PHQ-9 scores (EE = 0.12; 95% CI, 0.08 to 0.16; $P<.001$) but was only significantly different between the never tobacco users and current tobacco users (EE = 0.78; 95% CI, 0.05 to 1.51; $P=.04$). Overall

the smoking variable was not significant ($P=.110$) when considering all 3 groups (current, former and never), but when comparing the relationship between current and never smokers the difference was significant ($P=.04$). The WPI scores still increased with BMI (EE = 0.03 per kg/m^2 ; 95% CI, 0.001 to 0.06 per kg/m^2 ; $P=.040$) and were lower for those not taking opioid medications (EE = -1.08 ; 95% CI, -1.59 to -0.57 ; $P<.001$).

DISCUSSION

This cross-sectional retrospective study of 1068 patients with newly confirmed fibromyalgia revealed that tobacco use, sex, age, BMI, fibromyalgia-specific pharmacotherapy, and depression were associated with self-reported pain (WPI score) and symptom severity (SSS score). After adjusting for BMI, fibromyalgia-specific pharmacotherapy, sex, age, and depression, only tobacco status and age still retained significant associations with pain and symptom severity.

Numerous studies have demonstrated an association between smoking and pain, with smokers reporting more pain and worse functioning.^{8,22,23} A positive correlation has been observed between daily cigarette consumption and the intensity, frequency, and duration of widespread musculoskeletal pain,²⁴ rheumatoid arthritis,²⁵ fibromyalgia,²³ and oral pain.²⁶ It is estimated that the prevalence of smoking among individuals with pain is approximately 1.49 to 2.0 times greater than for the general population, indicating that about half the patients with chronic pain are smokers.²⁷ Individuals with a lifetime history of chronic pain are 1.95 to 2.30 times more likely to be current smokers with lifetime nicotine dependence.^{6,28} Smokers with chronic pain tend to be more adversely affected than nonsmokers, reporting greater pain intensity,²⁹ higher opioid consumption,³⁰ more sites of pain,²⁹ more severe functional impairment,³¹ and higher rates of substance abuse.³¹

In our study of patients with fibromyalgia, we found a higher WPI pain score (EE = 1.03) among current tobacco users compared with former and never tobacco users, as well as BMI (a measure of obesity), age, depression, and concomitant pain medication use. The association between tobacco use and age with

TABLE 2. Multiple Linear Regression With Outcome of Widespread Pain Index Score

	Estimate (95% CI) ^a	P
Intercept	12.79	
Type of smoker		.020
Current	1.03 (0.30 to 1.76)	
Former	0.26 (−0.32 to 0.84)	
Never	Reference	
Age (unit = 1 y)	−0.02 (−0.04 to −0.01)	.004
Sex		.343
Female	0.34 (−0.36 to 1.03)	
Male	ref	
Body mass index (unit = 1 kg/m^2)	0.04 (0.01 to 0.07)	.014
Fibromyalgia medications		.048
No medications	−0.48 (−0.95 to −0.01)	
Any medications	Reference	
Opioid medications		<.001
No medications	−1.16 (−1.68 to −0.64)	
Any medications	Reference	

^aFifty-one individuals were not included due to missing body mass index.

pain and symptom severity persisted even after controlling for all these factors.

These data are similar to a study of more than 400,000 veterans (50,988 women and 355,966 men) in which smoking alone was found to be associated with moderate to severe pain, after controlling for age, sex, obesity, substance abuse, mood disorder, post-traumatic stress disorder, and service-connected

TABLE 3. Multiple Linear Regression With Outcome of Pain Severity^a

	Estimate (95% CI)	P
Intercept	9.53	
Type of smoker		.036
Current	0.47 (0.11 to 0.84)	
Former	0.13 (−0.15 to 0.42)	
Never	Reference	
Age (unit = 1 y)	−0.02 (−0.02 to −0.01)	<.001
Sex		.517
Female	0.11 (−0.23 to 0.46)	
Male	Reference	
Body mass index (unit = 1 kg/m^2)	0.01 (−0.005 to 0.02)	.188
Fibromyalgia medications		.294
No medications	−0.13 (−0.36 to 0.11)	
Any medications	Reference	
Opioid medications		.050
No medications	−0.26 (−0.51 to 0.0)	
Any medications	Reference	

^aFifty-one individuals were not included due to missing body mass index.

TABLE 4. Multiple Linear Regression With Outcome of Widespread Pain Index (with PHQ-9)^{a,b}

	Estimate (95% CI)	P
Intercept	11.14	
Type of smoker		.110
Current	0.78 (0.05 to 1.51)	
Former	0.13 (−0.45 to 0.71)	
Never	Reference	
Age (unit = 1 y)	−0.02 (−0.03 to −0.001)	.037
Sex		.204
Female	0.45 (−0.24 to 1.14)	
Male	Reference	
Body mass index (unit = 1 kg/m ²)	0.03 (0.001 to 0.06)	.040
Fibromyalgia medications		.177
No medications	−0.32 (−0.80 to 0.15)	
Any medications	Reference	
Opioid medications		<.001
No medications	−1.08 (−1.59 to −0.57)	
Any medications	Reference	
PHQ-9 score (unit = 1)	0.12 (0.08 to 0.16)	<.001

^aPHQ-9 = Patient Health Questionnaire-9.

^bFifty-one individuals were not included due to missing body mass index, and 19 individuals were not included due to missing PHQ-9 scores.

disability.³² As with our study, this study of more than 400,000 veterans also found pain and symptom severity to be positively correlated to smoking status (current smoker, odds ratio [OR], 1.29) vs former smoker, OR, 1.02).³²

The association between chronic pain and smoking may reflect either the use of tobacco as a way to cope with pain,^{12,33,34} continued smoking aggravating painful conditions,³³ or both. Smokers who are motivated to use tobacco to cope with or assuage pain may unwittingly aggravate their painful condition by increasing their cigarette consumption, thus entering into an endless cycle that could lead to greater nicotine dependence.³⁵ A 2006 cross-sectional study found that 18% of the respondents who had experienced significant pain in the past week reported using more cigarettes than those without significant pain and smoking was used for pain relief, compared with 4% who did not endorse significant pain.²⁸

Research has shown that smokers with chronic pain conditions report higher intensity pain than nonsmokers^{5,31,36,37} and use more opioid medication.^{30,38} A study of 239 patients who underwent surgery found that current and past smokers had a less-than-

expected decline in opioid use at 3 months postsurgery ($P<.05$).³⁸ All these studies reinforce the concept that smoking can alter the effectiveness of opioids prescribed for pain management. Accordingly, it has been proposed that “Smokers have higher pain scores and higher opioid use, but lower serum hydrocodone levels...[suggesting] an up-regulation of the metabolic pathway for morphine.”³⁹

Our data demonstrated that increases in age were associated with a decrease in reported pain (WPI) and symptom severity (SSS). This is consistent with a 2010 systematic review of 40 studies that showed the association between smoking and current pain to be significantly higher among adolescents (OR, 1.82) vs adults (OR, 1.16).²⁷ Another study found that children exposed to smoking had significantly higher scores for pain compared with the nonexposed children ($P<.001$).⁴⁰ An analysis of 25,455 patients with spinal disorders across 23 health care facilities found that although smokers and nonsmokers had spinal symptoms of similar duration, smokers tended to be younger by about 4 years and report more severe pain (50% vs 37%, smokers to nonsmokers) that was present for a greater proportion of time and led to greater impairment, as demonstrated by lower physician and mental health scores and co-occurrence of depression (54% vs 37%, smokers to nonsmokers).⁴¹ In another study of 4490 people who reported musculoskeletal pain, it was found that after adjusting for age, sex, socioeconomic status, civil status, children younger than 16 years, physical exercise, presence of musculoskeletal disease, and mental distress, smokers experienced more intense pain than nonsmokers only if they were younger than 67 years (OR, 1.58).

In addition, smoking is associated with higher lifetime risk for musculoskeletal pain, an association that is stronger in younger patients because there are fewer possible confounding factors that often occur with aging.⁴² A survey study of 500 consecutive patients from an outpatient pain clinic found that smokers were younger, had higher pain intensity scores and Brief Pain Inventory functional impairment scores, and patients found to have severe nicotine dependence had significantly higher pain levels.³⁶

Nicotine has been shown to influence numerous central nervous system processes associated with fibromyalgia, including the serotonergic, noradrenergic, and dopaminergic neurotransmitter systems.⁵ Fibromyalgia, which is typically characterized by widespread pain, is believed to involve dysfunction of multiple pain modulatory systems in the brain. Dopamine is associated with both pain modulation and affective processing.⁴³ A study of 11 healthy females and 11 females who had fibromyalgia had each group undergo 2 infusions each of hypertonic saline solution and normal saline solution and found that patients with fibromyalgia reported a greater pain response to the hypertonic saline solution than did healthy control individuals. This finding correlated with decreased dopamine release in the basal ganglia during painful stimulation in patients with fibromyalgia as compared with their healthy controls. This abnormal dopamine response to pain may explain some of the increased sensitivities and pain experienced by patients with fibromyalgia.⁴⁴ This is further supported by reduced activity of the enzyme aromatic amino acid decarboxylase in some patients with chronic pain.⁴⁴ In addition, there is some evidence that alterations to aromatic amino acid decarboxylase may lower serotonin levels and heighten symptoms in patients with chronic pain.⁴⁵ These studies suggest that alterations in dopamine and serotonin metabolism might be related to clinical pain.

Potential mechanisms underlying increased pain among cigarette users include both direct effects on pain pathophysiology and indirect effects through overlap with symptoms of depression and anxiety.⁴⁶ Abnormal serotonin and norepinephrine levels have been described in patients who smoke, have depression, or experience chronic pain,⁴⁷ suggesting that common overlapping neurobiological factors likely influence the interaction. Medications that modulate central serotonin pathways (in addition to non-pharmacologic interventions such as cognitive behavioral therapy) are supported as evidence-based treatments of smoking cessation,⁴⁸ depression,^{49,50} and fibromyalgia.^{9,51,52} This supports the theory that pain, smoking, and anxiety/depression are all highly prevalent and comorbid and negatively affect mediators of reciprocal pain–smoking relations.¹¹

It has been hypothesized that smoking deprivation, either caused by a longer-than-usual time between periods of intake or attempts to quit, causes patients to have shorter pain latency.³⁹ A study of 5333 patients with axial and radicular pain secondary to spinal disorders found that compared with patients who had never smoked, current smokers reported significantly greater pain ($P < .001$) but reported a significant improvement if they quit smoking during their care vs those who continued smoking ($P < .05$).⁵³ This finding is further supported by a study of 497 patients treated in a multidisciplinary clinic for pain in which among former smokers, pain lessened as the duration of abstinence increased.²²

The endless cycle between smoking and pain is believed to be bidirectional in nature: current smoking has been associated with increased frequency and severity of pain,¹² but many patients with chronic pain cite smoking as a mechanism to help cope with the pain, increasing the likelihood for smokers with pain to be more heavily dependent on nicotine. This cycle may explain why smokers with pain have a more difficult time stopping smoking, with the occurrence of pain presenting as a barrier to stopping smoking.¹² Findings indicated that long-term smoking causes receptor desensitization, thereby amplifying the perception of pain severity in smokers.⁸ It is also believed that smoking interacts with central mechanisms, leading to worse pain outcomes in patients with fibromyalgia. A reciprocal model suggests that pain, smoking, and depression may positively feed back on each other, resulting in greater pain and the maintenance of tobacco dependence.⁵ A study of smokers' motivation to quit smoking found that smokers with chronic pain smoked more cigarettes per day, scored higher on the tobacco dependence scale, reported less confidence in their ability to quit, expected more difficulty in stopping smoking, and expected more severe withdrawal.¹²

As with our findings, the association of smoking and pain in patients with fibromyalgia is modified by the frequency of smoking, whereby current smokers had the highest association for more frequent and severe pain and symptoms, former smoking had a lower association, and never smoking had the lowest association. This is comparable to the findings

of a systematic review of 40 studies in which individuals who were current smokers had the highest rates of low back pain (OR, 2.14) as compared with former (OR, 1.32) and never smokers (OR, 1.31).²⁷ Our current data reinforce previous study data indicating the importance of smoking cessation among patients being managed for pain in a health care facility.

Our study has several limitations. First, most patients in our study were white, which is reflective of the referral population to our Midwest medical center, and therefore the generalizability of our findings to other racial and ethnic groups is limited. Second, although we observed associations with frequency and severity of pain and other symptoms and tobacco status, as well as the association of age with reported pain, we cannot speak to the reason for beginning or continuing to use tobacco (ie, coping with pain, self-medication for pain, or increased dependence to nicotine). In addition, we do not have complete data on the amount of tobacco used for current tobacco users, and although we were able to retrieve and analyze the WPI, SSS, and PHQ-9 (proxy for depression) scores, we were not able to access details of the other reported symptoms. Finally, one of the inherent limitations of retrospective studies is that we cannot determine directionality of the smoking-pain relationship but our findings reinforce the positive association between nicotine and pain, and previous data show plausible mechanisms for smoking to amplify pain perception, as well as benefit on pain perception with smoking cessation. Despite the acknowledged limitations, data from this study support the need to include a targeted tobacco cessation program for patients with fibromyalgia.

CONCLUSION

The results of our study suggest that tobacco use is associated with greater pain and other symptom severity in patients with fibromyalgia. Our study adds to the literature supporting the relationship between pain, symptom severity, and tobacco use. These findings have important clinical and research implications for patients with fibromyalgia who use tobacco. These same patients may benefit from early identification and timely implementation of tobacco cessation treatment

to decrease pain and improve overall quality of life.

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Abbreviations and Acronyms: BMI = body mass index; EE = effect estimate; EMR = electronic medical record; OR = odds ratio; PHQ-9 = Patient Health Questionnaire-9; SSS = Symptom Severity Scale; WPI = Widespread Pain Index

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