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Tobacco Smoking, Nicotine Dependence, and Patterns of Prescription Opioid Misuse: Results From a Nationally Representative Sample

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Abstract

Introduction: The misuse of prescription opioid medications is a growing public health crisis. Given evidence of complex nicotine-opioid interactions, and initial support for the role of smoking status as a risk factor for prescription opioid misuse, a more detailed analysis of how current and historical patterns of smoking may influence misuse of prescription opioids is warranted.

Methods: The current study is the first to test whether varying levels of current/historical smoking (current daily, current intermittent, former daily, never) and indices of smoking heaviness/nicotine dependence may be associated with greater likelihood of past-year prescription opioid misuse in the general population. Data were derived from the National Survey on Drug Use and Health (N = 24,348).

Results: Consistent with hypotheses, after accounting for sociodemographic factors and major depressive/alcohol use disorders, both daily and intermittent smokers were greater than 3 times more likely to report past-year nonmedical prescription opioid use than were never smokers. In addition, daily smokers were observed to be nearly 5 times more likely, and intermittent smokers were nearly 3 times more likely, to have met past-year abuse/dependence criteria, relative to never smokers. Results further revealed positive associations between various indices of smoking heaviness/nicotine dependence and opioid medication misuse, and these findings remained largely consistent when analyses were stratified by gender.

Conclusions: These findings indicate that smokers are not a homogeneous group with regard to risk for opioid misuse, and support the utility of comprehensive smoking assessment in the context of opioid-based treatment/tapering.

Introduction

The misuse of prescription opioid medications is a growing public health crisis that warrants greater empirical attention.[1] Although the term misuse may comprise a variety of aberrant behaviors, the current study focuses on nonmedical use (i.e., use for the feeling or experience, or use without a prescription) and diagnostic criteria for abuse/dependence (e.g., evidence of impaired functioning, tolerance, withdrawal). Factors that have been shown to confer heightened risk for prescription opioid misuse include the presence of chronic pain and co-occurring substance use/mood disorders.[2,3] Despite evidence of unique nicotine-opioid interactions,[4] surprisingly little research has examined tobacco smoking as a risk factor for the misuse of

prescribed opioids, and we are not aware of any studies that examined whether varying levels of tobacco consumption/dependence or having successfully quit smoking may confer differential risk for these outcomes.

There are several pathways by which unique nicotine-opioid interactions may confer greater risk for prescription opioid misuse. First, chronic nicotine exposure may result in dysregulation of the endogenous opioid system, leading to greater pain and cross-tolerance to prescription opioids.[4] There is also evidence that nicotine may sensitize the neural system to enhance the rewarding properties of opioid medications,[5] which is consistent with incentive-sensitization theories of addiction.[6,7] Although there is initial evidence that smoking may be associated with nonmedical use of prescribed opioids,[8–10] each of these studies utilized fairly "crude measures of smoking" (Skurtveit, Furu, Selmer, Handal, and Tverdal[11], p. 893) over the past year (i.e., any vs. none) that were included along with numerous other factors in large statistical models. While this approach has utility in the identification of risk factors that warrant further empirical scrutiny, such narrow classifications infer homogeneity and may obscure important differences both within current smokers (e.g., as a function of daily cigarette consumption or age at smoking onset) and between current smokers, those who previously smoked but quit, and never smokers. Indeed, evidence of substantive differences between heavy and light or intermittent smokers (e.g., smoking motives; Shiffman, Dunbar, Scholl, and Tindle[12]) underscores the need to conduct research among samples that represent a spectrum of smoking patterns (i.e., smoking frequency, intensity, and duration; Fagan and Rigotti[13]).

Considering the societal and economic costs associated with an escalating prescription opioid epidemic,[14] additional studies designed to explicate patterns of misuse in the general population are sorely needed.[1] Evidence of complex nicotine-opioid interactions, along with initial support for the role of smoking status in the prediction of prescription opioid misuse, warrants a more detailed analysis of how current and historical patterns of smoking may influence these outcomes. Indeed, we are aware of only one population-based study that examined relations between nicotine dependence and misuse of prescribed opioids,[15] though these analyses were limited to lifetime diagnostic criteria, and failed to account for co-occurring mood and substance use disorders. Additional support for a more detailed examination of smoking characteristics in relation to prescription opioid misuse can be derived from studies that found heavier smokers (relative to lighter and never smokers) used analgesic medications more frequently[16] and held a greater number of opioid prescriptions.[11,17] We are not, however, aware of any previous studies that tested associations between varying levels of tobacco smoking and prescription opioid misuse outcomes.

The main goal of the current study was to assess the extent to which varying levels of current and historical nicotine/tobacco exposure (i.e., current daily vs. current intermittent vs. former daily vs. never smoking) may be differentially associated with past-year opioid misuse, after accounting for relevant sociodemographic characteristics and the presence of past-year major depression and alcohol use disorders. A second goal was to examine indices of smoking heaviness/nicotine dependence in relation to past-year opioid misuse among our nationally representative sample of current daily smokers. Specifically, we hypothesized that the greatest likelihood for both nonmedical use and abuse/dependence on prescribed opioids would be observed among current daily smokers, followed by intermittent and former smokers, relative to never smokers. We further hypothesized that, among current daily smokers, greater cigarette consumption, higher nicotine dependence scores, and earlier age at initiation of smoking would each be positively associated with past-year opioid misuse outcomes. Finally, consistent with previous research,[8,10] we examined each of these outcomes stratified by gender.

Methods

Data Source

Data were derived from the 2009 National Survey on Drug Use and Health (NSDUH). The NSDUH is a nationally representative survey of persons age 12 and older who reside in the United States (total N = 68,700). Recruitment, sampling, and interviewing procedures have been previously described.[18] The current analyses were restricted to data obtained from adult respondents who were classified as current daily, current intermittent, former daily, or never smokers (N = 24,348).

Measures

Nonmedical Prescription Opioid Use

Nonmedical prescription opioid use was defined by either use without holding a prescription, or for the experience/feeling that it produced. Respondents viewed a card with pictures and names of prescription pain relievers, and were asked to indicate (yes/no) whether they had used each in a nonmedical fashion over the past year. Medication names provided on the card corresponded with pictures of the capsules/tablets, such that pictures of brand name medications were labeled with the registered brand name (e.g., OxyContin® or Percocet®), and pictures of generic medications were labeled with the name of the medication (e.g., morphine, codeine). Respondents who endorsed nonmedical use of at least one prescription opioid were considered positive for past-year nonmedical opioid use.

Prescription Opioid Abuse/Dependence

Past-year prescription opioid abuse and dependence were assessed using Diagnostic and Statistical Manual criteria (DSM-IV).[19] Given that prior research has typically combined abuse/dependence,[8,9] and that DSM-V criteria no longer distinguishes abuse from dependence,[20] we utilized a composite variable provided by NSDUH that represents the presence or absence of past-year opioid abuse/dependence.

Smoking Status

Lifetime smoking status was first screened with a single item ("Have you ever smoked part or all of a cigarette?"). A response of "yes" prompted additional questions regarding frequency of smoking, number of cigarettes smoked per day, and age at smoking onset. Responses were used to calculate a composite smoking status variable as follows: current daily smokers (smoked every day for the past 30 days), former daily smokers (prior daily smoking but no smoking in the past year), intermittent smokers (smoked 4–27 days of the past month and never smoked daily; Shiffman et al.[12]), and never smokers (never smoked all or part of a cigarette).

Number of Cigarettes Smoked per Day

Respondents who endorsed past-month smoking were asked: "On the days you smoked cigarettes during the past 30 days, how many cigarettes did you smoke per day, on average?" Responses were coded by the NSDUH into a categorical item representing fewer

than 6, 6–15, 16–25, or 26 or more. Consistent with prior research that utilized 15 cigarettes per day (cpd) as a cut-off to delineate light from moderate/heavy smokers,[21,22] cpd was dichotomized (≤15 or >15).

Nicotine Dependence

Nicotine dependence was assessed using an item from the Fagerström Test of Nicotine Dependence that asked smokers to indicate how soon after waking they have their first cigarette of the day.[23] Time to first cigarette is considered a valid measure of physiological dependence on nicotine/tobacco,[24] and has been related to biochemical markers of tobacco use (i.e., continine; Muscat, Stellman, Caraballo, and Richie[25]) and smoking cessation outcomes.[26] Consistent with prior research,[25,27] responses were dichotomized as being indicative of either high (i.e., smoking within 30 min of waking) or low (i.e., smoking more than 30 min after waking) dependence.

Age of Smoking Onset

Respondents were asked: "How old were you the first time you smoked part or all of a cigarette?" Responses were coded by the NSDUH into a categorical item representing age of onset at 14 years or younger, 15–17 years, 18 years or older, or nonusers.

Sociodemographic Characteristics and Psychiatric Comorbidity

Previous research indicates that several factors may be relevant to smoking-opioid use relations, including various sociodemographic characteristics and co-occurring depression and alcohol use disorders.[8,9,28,29] Therefore, from an a priori basis, all analyses statistically-controlled for age, marital status, education, employment status, gender, race/ethnicity, past-year major depressive episode (MDE), and past-year alcohol use disorder (AUD). Past-year MDE and AUD were diagnosed according to DSM-IV criteria.[19]

Data Analytic Plan

Analyses were conducted in SAS 9.4 using PROC SURVEYLOGISTIC, and utilized weights provided by NSDUH.[18] First, we constructed a set of logistic regression models with smoking status entered as the fixed factor, and past-year nonmedical prescription opioid use and past-year prescription opioid abuse/dependence entered as the respective dependent variables. We then constructed a second set of logistic regression models to test associations between indices of nicotine dependence (i.e., age at initiation of smoking, nicotine dependence scores, and number of cigarettes smoked per day) and past-year nonmedical opioid use and abuse/dependence, among our subsample of current daily smokers (n = 6,922). Analyses included never smokers as the reference group. To test whether the smoking variables were uniquely associated with nonmedical prescription opioid use and abuse/dependence, above-and-beyond the variance attributed to other relevant factors, all regression models controlled for sociodemographic characteristics, MDE, and AUD. Consistent with prior research that utilized data derived from the NSDUH, we then conducted separate logistic regression models, stratified by gender, to determine whether associations were consistent across males and females.[8,10]

Results

Sample Characteristics

Of the adult respondents meeting criteria for one of the smoking categories (N = 24,348), 24.1% were categorized as current daily smokers, 25.9% as former daily smokers, 3.5% as intermittent smokers, and 46.5% as never smokers. As seen in Table 1, slightly more than half of all respondents were male (52.5%), married (53.9%), and currently employed (61.3%). Nearly 70% of the sample identified as non-Hispanic White, and greater than 80% had graduated from high school. Consistent with previous research derived from nationally representative surveys, 4.3% of all respondents endorsed past-year nonmedical prescription opioid use (e.g., 4.5%–5.1%; Back et al.[8]; Becker et al.[9]), 0.7% met criteria for past-year opioid abuse/dependence (e.g., 0.7%; Back et al.[8]), and 6.5% met criteria for a past-year major depressive episode (e.g., 6.7%; Kessler, Chiu, Demler, Merikangas, and Walters[30]).

Associations Between Current/Historical Smoking Status and Prescription Opioid Misuse

Past-Year Nonmedical Prescription Opioid Use

As hypothesized, among the total sample, both daily (AOR = 3.79, 95% CI = 3.00–4.79, p < .001) and intermittent smokers (AOR = 3.12, 95% CI = 2.32–4.18, p < .001) were over three times more likely than never smokers to have endorsed past-year nonmedical prescription opioid use (Table 2). No differences were observed between former and never smokers (p = .44). A similar pattern of results was observed when analyses were stratified by gender, such that both daily and intermittent (ps < .001), but not former (ps > .44) smoking were associated with a greater likelihood of past-year nonmedical use of prescription opioids among both men and women (Table 3).

Past-Year Prescription Opioid Abuse/Dependence

As hypothesized, among the total sample, daily smokers were nearly five times more likely (AOR = 4.82, 95% CI = 2.46–9.43, p < .001), and intermittent smokers were nearly three times more likely (AOR = 2.96, 95% CI = 1.13–7.78, p = .03), to have met criteria for past-year abuse/dependence, relative to never smokers. We did not observe any differences between former and never smokers (p = .39). When analyses were stratified by gender, results indicated that both male and female current daily smokers (relative to never-smokers) were more likely to have met criteria for past-year abuse/dependence (ps < .01). Among females only, former daily smokers were also more likely to have met criteria for opioid abuse/dependence in the past-year (p = .008), relative to never smokers.

Associations Between Indices of Smoking Heaviness/Nicotine Dependence and Prescription Opioid Misuse Among Current Daily Smokers

Past-Year Nonmedical Prescription Opioid Use

As hypothesized, among the total sample, current daily smokers who reported smoking onset prior to age 14 were more than twice as likely to have endorsed past-year nonmedical use of prescribed opioids (AOR = 2.32, 95% CI = 1.56–3.44, p < .001), relative to those who began smoking after age 18. A similar pattern of results was observed when analyses were stratified by gender, such that smoking onset prior to age 14 was associated with an increased likelihood of past-year opioid misuse among both males and females (ps < .01). Results also indicated that smoking greater than 16 cpd (vs. ≤15 cpd) was associated with an increased likelihood of past-year nonmedical opioid use among females (AOR = 1.79, 95% CI = 1.27–2.53, p = .001), but not in the total sample or among males (ps > .08). Finally, no associations were observed between nicotine dependence

Table 1. Sample Demographics by Smoking Status

	Total sample *N* (%)	Current daily smokers, *n* (%)	Former smokers, *n* (%)	Intermittent smokers, *n* (%)	Never smokers, *n* (%)
Past-year nonmedical opioid use					
Yes	1,812 (4.3)	1,132 (10.5)	125 (1.8)	217 (11.5)	338 (1.9)
No	22,536 (95.7)	5,790 (89.5)	3,516 (98.2)	1,206 (88.5)	12,024 (98.1)
Past-year opioid abuse or dependence					
Yes	338 (0.7)	265 (2.1)	14 (0.3)	23 (1.6)	36 (0.2)
No	24,010 (99.3)	6,657 (97.9)	3,627 (99.7)	1,400 (98.4)	12,326 (99.8)
Past-year MDE					
Yes	1,877 (6.5)	834 (11.0)	254 (6.2)	114 (8.9)	675 (4.2)
No	22,271 (94.5)	6,017 (89.0)	3,375 (93.8)	1,296 (91.1)	11,583 (95.8)
Past-year AUD					
Yes	2,427 (6.7)	1,306 (13.7)	234 (4.9)	364 (22.0)	523 (3.0)
No	21,921 (93.3)	5,616 (86.3)	3,407 (95.1)	1,059 (78.0)	11,839 (97.0)
Age					
18–29	13,473 (20.4)	3,956 (24.6)	719 (5.3)	1,156 (51.5)	7,642 (24.4)
30–49	6,888 (34.9)	2,187 (42.1)	1,389 (27.9)	224 (34.5)	3,088 (35.2)
50+	3,987 (44.6)	779 (33.4)	1,533 (66.9)	43 (14.0)	1,632 (40.4)
Sex					
Female	11,109 (47.5)	3,535 (51.1)	1,785 (45.0)	581 (38.8)	7,338 (59.9)
Male	13,239 (52.5)	3,387 (48.9)	1,856 (55.0)	842 (61.2)	5,024 (40.1)
Race/ethnicity					
White	15,161 (67.5)	5,221 (79.4)	2,870 (82.8)	735 (48.8)	6,335 (54.2)
Black	3,265 (12.0)	597 (9.3)	225 (6.5)	250 (19.2)	2,193 (16.0)
Hispanic	3,729 (13.6)	545 (7.7)	322 (7.2)	315 (25.7)	2,547 (19.2)
Other	2,193 (6.9)	559 (3.6)	224 (3.4)	123 (6.3)	1,287 (10.6)
Marital status					
Married	8,553 (53.9)	1,973 (41.5)	2,219 (67.8)	186 (27.0)	4,175 (54.5)
Unmarried	15,795 (46.1)	4,949 (58.5)	1,422 (32.2)	1,237 (73.0)	8,187 (45.5)
Education					
Less than high school	4,649 (17.5)	1,742 (21.9)	527 (13.6)	279 (18.6)	2,101 (17.4)
At least high school	19,699 (82.5)	5,180 (78.1)	3,114 (86.4)	1,144 (81.4)	10,261 (82.6)
Employment					
Employed	15,662 (61.3)	4,439 (64.6)	2,361 (56.8)	959 (69.2)	7,903 (61.5)
Not employed	8,686 (38.7)	2,483 (35.4)	1,280 (43.2)	464 (30.8)	4,459 (38.5)

Note. Results are reported as unweighted *N* and weighted percentages. AUD = alcohol use disorder; MDE = major depressive episode.

scores and past-year nonmedical prescription opioid use in the total sample or when analyses were stratified by gender (*p*s > .08).

Past-Year Prescription Opioid Abuse/Dependence

Also as hypothesized, current daily smokers who scored high (relative to low) on the nicotine dependence item were more than twice as likely to have met past-year prescription opioid abuse/dependence criteria in the total sample (*AOR* = 2.51, 95% CI = 1.57–4.00, $p < .001$), and among both males and females (*p*s < .01). Current daily smokers who reported smoking greater than 16 cpd (relative to those who smoked ≤15 cpd) were also more likely to have met diagnostic criteria for past-year prescription opioid abuse/dependence in the total sample (*AOR* = 1.96, 95% CI = 1.21–3.17, $p = .006$) and among females ($p = .007$). Finally, we observed no association between age of smoking onset and past-year prescription opioid abuse/dependence in the total sample or when analyses were stratified by gender (*p*s > .08).

Discussion

Despite initial evidence that tobacco smoking may confer increased risk for the nonmedical use of prescribed opioids,[8–10] and increasing awareness of unique nicotine-opioid interactions,[4] we are not aware of any previous studies that examined the extent to which varying levels of current and historical nicotine/tobacco exposure may be differentially associated with likelihood of past-year prescription opioid misuse. Consistent with hypotheses, these data revealed that both daily and intermittent smokers were greater than three times more likely than never smokers to have engaged in nonmedical use of prescribed opioids over the past year. These data further revealed that, relative to never smokers, daily smokers were nearly five times more likely, and intermittent smokers were nearly three times more likely, to have met diagnostic criteria for past-year prescription opioid abuse/dependence, even after accounting for relevant sociodemographic characteristics and the presence of past-year major depressive/alcohol use disorders. The pattern of results observed among the total sample remained largely consistent when analyses were stratified by gender, which suggests that varying levels of tobacco smoking are associated with prescription opioid misuse among both males and females. To our knowledge, this is the first population-based study to observe an association between positive smoking status and increased likelihood for prescription opioid abuse/dependence.

It is also noteworthy that, among females only, former daily smokers were more likely to have met criteria for past-year prescription opioid abuse/dependence, relative to never smokers. Thus, for

Table 2. Past-Year Nonmedical Opioid Use and Abuse/Dependence Among Respondents Aged 18 and Older

	Past-year nonmedical opioid use			Past-year opioid abuse/dependence		
	AOR	95% CI	*p* value	*AOR*	95% CI	*p* value
Smoking status						
Never smoker	ref					
Current daily smoker	3.79	3.00–4.79	<.001	4.82	2.46–9.43	<.001
Former daily smoker	1.18	0.81–1.72	.39	1.46	0.59–3.64	.42
Intermittent smoker	3.12	2.32–4.18	<.001	2.96	1.13–7.78	.03
Past-year MDE						
No	ref					
Yes	2.44	1.88–3.17	<.001	3.55	2.33–5.43	<.001
Past-year AUD						
No	ref					
Yes	2.81	2.26–3.50	<.001	3.54	2.34–5.36	<.001
Age						
18–29	ref					
30–49	0.43	0.41–0.60	<.001	0.63	0.41–0.97	.04
50+	0.23	0.16–0.32	<.001	0.21	0.11–0.42	<.001
Sex						
Female	ref					
Male	1.31	1.09–1.57	.004	1.45	0.98–2.14	.06
Race/ethnicity						
White	ref					
Black	0.43	0.30–0.61	<.001	0.16	0.07–0.33	<.001
Hispanic	0.58	0.44–0.77	.001	0.66	0.33–1.31	.23
Other	0.82	0.50–1.33	.41	0.74	0.18–3.04	.67
Marital status						
Unmarried	ref					
Married	0.68	0.55–0.84	<.001	0.69	0.43–1.10	.12
Education						
<High school	ref					
≥High school	0.86	0.69–1.07	.17	0.66	0.42–1.04	.07
Employment						
Employed	ref					
Unemployed	1.22	1.01–1.48	.04	1.86	1.26–2.75	.002

Note. AOR = adjusted odds ratio; AUD = alcohol use disorder; MDE = major depressive episode.

women in our sample, successful smoking cessation was not associated with a reduced likelihood of opioid abuse/dependence. Within the total sample and among males, we observed no differences in prescription opioid misuse between former and never smokers. Whereas this null finding might be interpreted to suggest that successful quitting may reduce liability for misuse of prescribed opioids, it is equally plausible that these former smokers may have been less dependent on both nicotine and opioid medications in the first place.

Consistent with the notion that tobacco and prescription opioid dependence may covary, the current results also revealed positive associations between several indices of nicotine dependence and likelihood of past-year opioid medication misuse. As hypothesized, in the total sample, current daily smokers who initiated tobacco use prior to age 14 (compared to after age 18) were more than twice as likely to have endorsed past-year nonmedical use of prescribed opioids. In addition, those who either reported smoking greater than 15 cpd or scored high (relative to low) on a measure of nicotine dependence were approximately two times more likely to have met criteria for past-year prescription opioid abuse/dependence. Interestingly, when analyses were stratified by gender, results indicated that smoking greater than 15 cpd was associated with increased likelihood of both past-year prescription opioid nonmedical use and abuse/dependence among females only. These results suggest that, particularly among females, greater levels of cigarette consumption may be an important factor to consider in assessment of prescription opioid misuse.

Prescription opioid misuse is a growing public health crisis. In 2010, there were greater than 22,000 prescription drug overdose deaths, and 75% involved opioid pain medications.[31] Unfortunately, the identification of factors that reliably and accurately predict prescription opioid misuse has proven to be an empirical and clinical challenge.[3] For example, challenges in this area include both the identification of misuse among those who hold prescriptions for opioid medications, and the identification of nonmedical opioid use among those who obtain the medications without a prescription (e.g., purchased illegally). Results of the current study extend previous findings that current smoking may be associated with increased utilization of prescription opioids,[11,17] by indicating that heavier, more nicotine-dependent smokers may be at greater risk to misuse opioid medications than lighter, less-nicotine dependent smokers.

There are several mechanistic pathways by which tobacco smoking may be associated with the onset and maintenance of prescription opioid misuse. First, chronic nicotine exposure may result in dysregulation of the endogenous opioid system, leading to greater pain and cross-tolerance to opioid medications.[4] As such, smokers tend to require greater doses of analgesic medications,[32,33] and we suspect that greater pain, cross-tolerance to

Table 3. Associations Between Smoking Variables and Prescription Opioid Misuse Stratified by Gender

	Male			Female		
	AOR	95% CI	*p* value	*AOR*	95% CI	*p* value
Outcome variable: past-year nonmedical prescription opioid use						
Smoking status						
Never	ref			ref		
Daily	4.33	2.96–6.36	<.001	3.28	2.48–4.38	<.001
Former	1.17	0.65–2.12	.60	1.20	0.75–1.91	.44
Intermittent	3.53	2.32–5.37	<.001	2.81	1.78–4.41	<.001
Age of smoking onset						
>18 years	ref			ref		
15–17 years	1.14	0.67–1.94	.63	1.93	0.98–3.81	.06
<14 years	2.17	1.32–3.57	.002	2.46	1.29–4.70	.006
CPD						
≤15	ref			ref		
>15	0.98	0.69–1.40	.92	1.79	1.27–2.53	.001
Nicotine dependence						
Low	ref			ref		
High	1.18	0.86–1.62	.32	1.27	0.89–1.81	.18
Outcome variable: past-year prescription opioid abuse/dependence						
Smoking status						
Never	ref			ref		
Daily	3.26	1.35–7.88	.009	8.46	3.94–18.18	<.001
Former	0.64	0.16–2.59	.06	4.07	1.44–11.50	.008
Intermittent	3.10	0.96–10.06	.53	1.74	0.49–6.27	.39
Age of smoking onset						
>18 years	ref			ref		
15–17 years	1.60	0.61–4.18	.34	0.60	0.13–2.76	.67
<14 years	2.19	0.91–5.21	.08	1.35	0.33–5.50	.52
CPD						
≤15	ref			ref		
>15	1.86	0.87–3.97	.11	2.28	1.26–4.13	.007
Nicotine dependence						
Low	ref			ref		
High	2.62	1.29–5.31	.007	2.50	1.32–4.75	.005

Note. Individual logistic regression models were constructed for each respective smoking variable. Age of smoking onset, cpd, and nicotine dependence were tested only among respondents who endorsed current daily smoking. *AOR* = adjusted odds ratio, after controlling for past-year major depressive episode, past-year alcohol use disorder, age, race/ethnicity, marital status, education, and employment; CPD = cigarettes per day.

opioid medications, and diminished pain relief could motivate escalation of opioid consumption among smokers. There is also some evidence from animal models that exposure to nicotine may enhance the rewarding/reinforcing properties of prescription opioids.[5] Reward and reinforcement processes are well-represented in theories of addiction,[34] and according to Incentive Sensitization Theory, repeated drug administration may not only render the neural system hypersensitive to the effects of that drug, but can also produce cross-sensitization to other substances.[6] Indeed, the rewarding effects of both nicotine and opioid medications are thought to be partially mediated by the dopaminergic system, and there is some evidence that chronic nicotine exposure may sensitize the dopaminergic system to opioid-based medications.[5] Thus, over time, tobacco smokers may become sensitized to enhanced reward/reinforcement from prescription opioids, which could in turn contribute to opioid misuse among smokers. Finally, it has been suggested that associations between smoking and prescription opioid misuse may covary as a function of co-occurring risk factors such as depression and other substance use.[2] However, in the current study, associations between smoking status/heaviness and prescription opioid misuse persisted after controlling for past-year major depressive and alcohol use disorders.

The current findings may have clinical relevance for smokers with chronic pain who are maintained on opioid therapy, as they have been shown to report more severe pain and to require greater doses of opioid analgesics, relative to nonsmokers.[32,33] Treatment-seeking pain patients who endorse smoking to cope with pain have evinced greater reliance on opioid medications,[35] and smokers (compared to nonsmokers) may be less likely to complete pain treatment that requires opioid tapering.[36] In addition, there is some evidence that smoking behavior may be influenced by consumption of prescription opioids,[37] and persons who use opioid medications for pain management may be more likely to smoke tobacco.[38] Collectively, these data are consistent with a recently proposed reciprocal model of pain and smoking (for review, see Ditre, Brandon, Zale, and Meagher[39]), which posited that chronic pain, continued smoking, and the use/misuse of prescription opioids may interact to maintain pain and impede smoking cessation.

Strengths of the current study include use of a large and nationally representative sample, multilevel analysis of current and historical smoking patterns, and the utilization of established diagnostic criteria for past-year prescription opioid abuse/dependence. Several limitations also bear noting. First, these cross-sectional data preclude causal inferences and cannot establish temporal precedence with

regard to smoking onset/cessation and the use/misuse of prescribed opioids. Second, smoking status was not biochemically verified, and though former smokers reported being abstinent for at least one year, the exact duration since quitting was not known. Third, given that chronic pain was not assessed in the NSDUH, these findings may not generalize to all smokers with chronic pain who have received prescriptions for opioid medications. However, chronic pain and smoking are highly comorbid,[39] and these data may be representative of a broader segment of the smoking population that is likely to have experienced pain. These findings may also be representative of the broader population of persons who misuse prescription opioids, including those who use these medications without holding a prescription.

In summary, results of the current study indicate that "current smokers" are not necessarily a homogenous group with regard to likelihood of past-year opioid medication misuse, and that indices of nicotine dependence and smoking heaviness may have utility in differentiating misuse liability among current smokers. These results also suggest that the likelihood of prescription opioid misuse may not be elevated among males who successfully abstained from tobacco smoking. However, among females, former daily smokers were more likely to have met criteria for opioid abuse/dependence, which underscores the importance of a detailed smoking assessment that includes both current and historical tobacco use. Indeed, these data support the utility of more comprehensive assessment of smoking in clinical pain treatment settings, and in the context of studies that examine interrelations between pain reporting and the self-administration of prescribed opioids. These data also contribute to an emerging literature that may ultimately explicate potentially unique and reciprocal relations between tobacco smoking and the misuse of prescription opioid medications. Future research should examine whether smokers maintained on opioid therapy develop tolerance more quickly than nonsmokers, and whether smoking independently predicts use of opioids for its rewarding properties. Future research would also benefit from testing real-time associations between tobacco smoking and the consumption/perceived utility of opioid medications, perhaps using ecological momentary assessment.[40] Additional research may also benefit from examining relevant cognitive constructs that could help to explain the co-occurring use of both nicotine and prescription opioids (e.g., distress tolerance, impulsivity, and delay discounting). Finally, it would be interesting to examine prospective relations between smoking cessation/relapse, pain severity, and the consumption/perceived efficacy of prescription opioids.

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Declaration of Interests

None declared.

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