Psychology of Addictive Behaviors

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Although smokers with co-occurring pain report expectations for experiencing greater nicotine withdrawal and difficulty quitting, limited work has examined the role of pain in cessation-related outcomes. The goal of this study was to examine clinically relevant pain characteristics (pain persistence, pain intensity, pain-related disability) as predictors of withdrawal and smoking lapse/relapse outcomes using a laboratory paradigm of cessation. Participants (N = 120 daily cigarette smokers; 48% male; M_{age} = 36.17, SD = 12.16; $M_{\text{Cigarettes Per Day}}$ = 20.51, SD = 6.99) were randomized to either nondeprived or 12-hr nicotine deprivation conditions prior to an experimental study visit. Upon arrival to the laboratory, participants completed measures of pain characteristics and nicotine withdrawal symptoms. Primary outcomes included nicotine withdrawal scores and analogues of smoking lapse (latency to initiating smoking) and relapse (number of cigarettes smoked). We hypothesized that smokers with greater pain persistence, pain intensity, and pain-related disability would endorse more severe nicotine withdrawal and greater lapse/relapse behavior, and that these positive associations would be stronger among those who were nicotine deprived. Results indicated that, above and beyond the effect of nicotine deprivation, persistent pain predicted more severe nicotine withdrawal, and that greater pain-related disability predicted quicker latency to lapse during the laboratory paradigm. Contrary to expectation, nicotine deprivation did not moderate effects of pain characteristics on withdrawal or lapse/relapse outcomes. Clinical implications include that different pain processes may influence different cessation outcomes, and that smokers in pain may benefit from the provision of pharmacological aids to better control withdrawal symptoms.

Keywords: smoking, smoking cessation, nicotine withdrawal, pain, pain-related disability

Pain and tobacco cigarette smoking are highly prevalent and co-occurring conditions that engender a combined annual economic burden of $900 billion in the United States alone (Gaskin & Richard, 2012; Sacks, Gonzales, Bouchery, Tomedi, & Brewer, 2015). Although the prevalence of smoking in the general population has declined to 14% over the past 2 decades (Norris, Schiller, & Clarke, 2018), this trend has not been observed among pain patients (Orhurhu, Pittelkow, & Hooten, 2015). Indeed, rates of current smoking among individuals with pain have remained up to two times greater than in the general population (Michna et al., 2004; Zvolensky, McMillan, Gonzalez, & Asmundson, 2009). Accumulating research further suggests that the prevalence and intensity of pain is higher among smokers than nonsmokers (Bakhshaie et al., 2016; Johannes, Le, Zhou, Johnston, & Dworkin, 2010; Palmer, Syddall, Cooper, & Coggon, 2003).

An evolving reciprocal model posits that pain and smoking interact in the manner of a positive feedback loop, resulting in greater pain and maintenance of tobacco dependence (Ditre, Brandon, Zale, & Meagher, 2011; Ditre, Zale, & LaRowe, 2019; Zale, Maisto, & Ditre, 2016). Consistent with this model, converging evidence indicates that pain can be a potent motivator of tobacco smoking (Dhingra et al., 2014; Ditre & Brandon, 2008; Ditre, Heckman, Butts, & Brandon, 2010; Kosiba, Zale, & Ditre, 2018). Experimental pain induction has been shown to increase tobacco craving and withdrawal symptoms (Ditre & Brandon, 2008; Kotlyar et al., 2011; Parkerson & Asmundson, 2016), and ecological momentary assessment data further indicates that painful episodes often precede bouts of smoking (Dhingra et al., 2014). Smokers have reported using cigarettes to cope with pain (Hooten, Shi, Gazelka, & Warner, 2011), and given that nicotine confers acute

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analgesia (Ditre, Heckman, Zale, Kosiba, & Maisto, 2016), smokers with pain may attempt to self-medicate using cigarettes (Khantzian, 1987; Patterson et al., 2012). Preliminary research further suggests that pain may influence various cessation-related outcomes. Smokers with co-occurring pain (vs. without co-occurring pain) have been shown to report lower confidence in their ability to remain abstinent (Zale, Ditre, Dorfman, Heckman, & Brandon, 2014), hold expectations that they will experience more severe withdrawal during future quit attempts (Ditre, Kosiba, Zale, Zvolensky, & Maisto, 2016), and identify pain as a barrier to cessation (Ditre, Zale, Heckman, & Hendricks, 2017).

Despite emerging evidence supporting the notion that pain may undermine smoking cessation, no research to date has directly examined pain as a predictor of nicotine withdrawal during a quit attempt, and only three studies have examined associations between pain- and abstinence-related outcomes. First, greater sensitivity to prequit laboratory pain induction has been associated with a greater likelihood of early relapse to smoking (Nakajima & al'Absi, 2011). Second, greater pain-related anxiety (i.e., the tendency to respond to pain with anxiety or fear) has been shown to predict early lapse and relapse among smokers engaging a self-guided cessation attempt (LaRowe, Langdon, Zvolensky, Zale, & Ditre, 2017). Finally, among smokers with HIV, greater pain intensity was associated with a reduced likelihood of achieving 24-hr point prevalence abstinence (Aigner et al., 2017). Taken together, these initial findings suggest that pain and related constructs are associated with poorer cessation outcomes. However, these studies are limited in that they each examine only a single construct of pain (i.e., pain-related anxiety, sensitivity to experimental pain induction) or have been conducted among specific subpopulations.

There is growing recognition that approaches to characterizing pain should incorporate multidimensional indices, including measures of persistence (i.e., frequency of pain symptoms over a specific time period), intensity (i.e., reported intensity of pain symptoms), and disability (i.e., impact of pain on physical, occupational, recreation, and social functioning; Merskey & Bogduk, 1994; Thong, Jensen, Miró, & Tan, 2018; Turk & Melzack, 2011; Von Korff, Ormel, Keefe, & Dworkin, 1992). Moreover, there is reason to believe that each of these factors may differentially predict smoking cessation outcomes (e.g., Zale & Ditre, 2015), and several theoretical frameworks suggest that these pain characteristics may play an important role in the experience of withdrawal and relapse to smoking (Baker, Piper, McCarthy, Majeskie, & Fiore, 2004; Elman & Borsook, 2016; Simons, Elman, & Borsook, 2014). However, the predictive utility of these multidimensional indices have yet to be tested among smokers.

The goal of this secondary analysis was to test whether persistent pain, pain intensity, and pain-related disability each predict severity of self-reported nicotine withdrawal and lapse/relapse behavior among a sample of daily smokers (Heckman et al., 2017). We hypothesized that participants with persistent pain, high pain intensity, or moderate-to-severe pain-related disability would score higher on a measure of nicotine withdrawal symptoms, would demonstrate the fastest latency to first cigarette (i.e., lapse), and would smoke a greater number of cigarettes (i.e., relapse) during a laboratory paradigm of smoking cessation. We also examined whether nicotine deprivation (12 hr) moderated the hypothesized effects of pain characteristics on withdrawal, lapse, and relapse outcomes.

Method

Participants

Adult smokers were recruited from the Tampa, Florida, area via print and online advertisements for a primary experimental study examining the effects nicotine deprivation and self-control processes on lapse/relapse outcomes (Heckman et al., 2017). Prospective participants completed a telephone screener to determine eligibility. Inclusion criteria comprised speaking English, being 18–65 years old, smoking at least 15 cigarettes per day for at least 1 year, and providing a valid, stable mailing address and phone number. Exclusion criteria comprised concurrently using other nicotine or tobacco products, actively attempting to quit smoking, currently being pregnant, or having a hearing or visual impairment that would interfere with study procedures.

Procedure

All study procedures were approved by the Institutional Review Board at the University of South Florida. Randomization occurred prior to study recruitment, with 33 unique IDs assigned to each study condition and stratified by sex. In the event of no-shows or noncompliance with deprivation instructions, the condition assignment was recycled to allow for sample size quotas to be met. Following telephone screening, eligible participants were scheduled for a laboratory experimental session. Participants randomized to the nondeprived condition were instructed to smoke normally prior to their appointment and to smoke their last cigarette 5 min before arriving for their session. Participants randomized to the deprivation condition were instructed not to smoke or use any other nicotine products for 12 hr prior to their appointment. Upon arrival to the laboratory, participants provided informed consent and compliance with smoking instructions was verified via self-report and exhaled carbon monoxide (CO; i.e., nondeprived >11 ppm; deprived ≤ 11 ppm). A cut-off of ≤ 11 ppm has previously been used to verify 12-hr abstinence from cigarettes (Bello et al., 2018; Bidwell et al., 2013; Benowitz et al., 2002; Leventhal, Waters, Moolchan, Heishman, & Pickworth, 2010). Experimenters were not blind to deprivation condition assignment because they needed to verify compliance with preappointment instructions via exhaled CO. Participants who were compliant with the smoking instructions then completed baseline measures and a self-control depletion condition[1] (Heckman et al., 2017) before completing the laboratory paradigm of smoking cessation.

We used an established laboratory paradigm of smoking cessation that assesses lapse and relapse behavior during a single

[1] Participants were randomized to self-control depletion condition prior to arriving for their study visit. The self-control depletion manipulation involved watching a 6-min emotionally evocative video clip (participants were also informed they would be video recorded while viewing the clip). Those in the self-control depletion condition were asked to suppress any external emotions, whereas participants in the no self-control depletion condition were instructed to react naturally. Consistent with statistical guidelines supporting the covariation of variables associated with primary outcomes (Pocock et al., 2002), the self-control depletion manipulation was included as a covariate in all models examining lapse and relapse. Additionally, we observed no significant interactions between self-control depletion condition and pain characteristics on lapse/relapse outcomes ($ps > .320$).

session by providing financial incentives for abstinence from cigarettes (McKee, 2009; McKee, Weinberger, Shi, Tetrault, & Coppola, 2012). Participants were provided with a tray containing eight preferred brand cigarettes, an ashtray, and a lighter with instructions that they could begin smoking at any point over the next 50 min. They were also informed that they could earn $1 for every 5 min they delayed smoking, with a maximum payment of $10 over the 50-min period. The experimenter was not present in the room during the paradigm, but could be communicated with via a two-way intercom, and participants used the intercom to indicate if/when they wanted to smoke. Additionally, participants could be observed via a discrete camera. After the participant lit their first cigarette (or at the ending of the 50-min period), a 60-min self-administration period began where participants were instructed to "smoke as little or as much as you wish." In this paradigm, lapse behavior is assessed via the number of minutes participants maintain smoking abstinence during a 50-min period, and relapse behavior is assessed via the number of cigarettes smoked during a 60-min period following the initial lapse. Studies using this laboratory paradigm have verified antecedents to lapse and relapse commonly observed in treatment outcome research, such as acute nicotine deprivation (Leeman, O'Malley, White, & McKee, 2010; Leventhal et al., 2014), cigarette craving (Roche et al., 2014), anhedonia (Leventhal et al., 2014), and negative affect/stress (Leventhal et al., 2014; McKee et al., 2011). This paradigm has also been used to identify and screen potential cessation pharmacotherapies (Verplaetse et al., 2017) and behavioral interventions (Moody, Poe, & Bickel, 2017).

Measures

Smoking and sociodemographic characteristics. Participants completed a smoking history form that assessed daily cigarette consumption and smoking duration. Cessation self-efficacy was measured by averaging responses to three items that assessed confidence in the ability to quit smoking for a week, month, and year ($\alpha = .79$). Cigarette dependence was assessed using the Fagerström Test for Cigarette Dependence (FTCD; Fagerström, 2012; Heatherton, Kozlowski, Frecker, & Fagerström, 1991). Finally, participants self-reported information about sociodemographic characteristics (e.g., gender, race, education).

Nicotine deprivation manipulation check. Compliance with the deprivation manipulation was verified via self-reported time since last cigarette and presession expired CO concentration levels. Participants randomized to the deprivation condition (vs. nondeprived condition) were required to have a CO of $\leq$11 ppm (Leventhal et al., 2010). Nondeprived participants were required to have a CO level $>$11 ppm.

Nicotine withdrawal. The Minnesota Nicotine Withdrawal Scale (MNWS; Hughes & Hatsukami, 1986) was used to assess the severity of nine prototypical nicotine withdrawal symptoms over the past 12 hr (e.g., desire or craving to smoke) on a scale from 0 (*none*) to 4 (*severe*). Individual items were averaged to generate a total withdrawal severity score ($\alpha = .82$).

Pain characteristics. The Graded Chronic Pain Scale (Von Korff et al., 1992) generates three scales of pain persistence, pain intensity, and pain-related disability, and has been frequently used to assess pain among clinical and nonclinical samples (Turk & Melzack, 2011).

Pain persistence. The persistence classification score is based on a single item. Specifically, participants reported the number of days they had experienced pain in the past 180 days. Consistent with scoring recommendations, responses ranging from 90 to 180 days were classified as persistent pain ($\leq$89 days = no persistent pain; Von Korff et al., 1992).

Pain intensity. The characteristic pain intensity score was computed by summing responses to three questions that asked participants to rate their pain "right now," "on average," and at its "worst" in the past three months on an 11-point scale (0 = *no pain* to 10 = *pain as bad as it could be*). Total characteristic pain intensity scores ranged from 0 to 30. Consistent with previous work, participants were grouped according to their characteristic pain intensity ($>$15 = none-to-low intensity vs. $\leq$15 high intensity; Adams et al., 2018; Urquhart, Shortreed, Davis, Cicuttini, & Bell, 2009).

Pain-related disability. To calculate the pain-related disability score, we summed responses from three items assessing interference of pain with daily functioning over the past 3 months on an 11-point scale (0 = *no interference* to 10 = *unable to carry on any activities*), and one item measuring the number of days pain interfered with usual activities on an 11-point scale (0 = *none* to 10 = *76–90 days*). Total disability scores ranged from 0 to 40. Consistent with previous work (Ozdemir-Karatas, Peker, Balık, Uysal, & Tuncer, 2013), pain-related disability status was dichotomized ($>$24 = none-to-low vs. $\leq$24 = moderate-to-severe).

Data Analytic Plan

All analyses were conducted using SPSS Statistics 24. First, χ^2 and *t* tests were used to determine differences in sociodemographic factors, pain, and smoking characteristics as a function of the nicotine deprivation manipulation. Second, we ran a series of bivariate correlations for continuous variables and point biserial correlations for dichotomous variables to test zero-order associations between pain characteristics, potential covariates (sociodemographic factors, smoking characteristics) and outcomes (MNWS scores, time to first cigarette, and number of cigarettes smoked). Variables that differed as a function of the deprivation manipulation or were correlated with primary outcomes were retained as covariates in all subsequent analyses (Pocock, Assmann, Enos, & Kasten, 2002). Second, we tested differences in withdrawal severity (MNWS scores) as a function of persistent pain, pain intensity, and pain-related disability using three separate analysis of covariance (ANCOVA) models. In each model, we included a Deprivation Condition × Pain Characteristic interaction term. Third, we used the Cox proportional hazards model to estimate risk of lapse behavior as a function of persistent pain, pain intensity, and pain-related disability. The Cox model has been used to identify predictors of lapse outcomes during the laboratory paradigm of smoking cessation (Roche et al., 2014). Consistent with previous research, individuals who did not smoke during the 50-min delay period were censored (Roche et al., 2014). Three separate models were conducted with variables entered in the following steps: Step 1, covariates; Step 2, pain characteristics (persistent pain, pain intensity, or pain-related disability) and nicotine deprivation condition; Step 3, Pain Characteristic × Nicotine Deprivation interaction term. Fourth, Kaplan–Meier survival curves were used to compare trajectories to lapse as a function of persistent pain, pain intensity, and pain-related disability. Differences in survival curves were tested using the log-rank test (Goel, Khanna, & Kishore, 2010), with a significant log-rank result ($p < .05$) indicating that the trajectory to lapse behavior differs based on group status. Finally, three separate ANCOVAs examined effects of persistent pain, pain intensity, and pain-related disability on relapse behavior (i.e., number of cigarettes smoked). All models included a Pain Variable × Nicotine Deprivation interaction term.

Results

Participant Characteristics

Sociodemographic and smoking history data are presented in Table 1. Participants included 120 current daily tobacco smokers (48% male; $M_{age} = 36.2$, $SD = 12.2$) who reported smoking approximately 20 cigarettes per day ($SD = 7.0$) for an average of 17 years ($SD = 10.9$). The mean FTCD score was 5.7 ($SD = 1.9$), indicating a moderate level of tobacco dependence (Heatherton et al., 1991). The sample was predominantly white (75%), single (59%), and approximately 33% had completed some college. Almost half of all participants (44%) reported earning less than $10,000 per year. Approximately 25% of the sample endorsed persistent pain ($n = 31$), almost 40% reported high pain intensity ($n = 47$), and about 26% endorsed moderate-to-severe pain-related disability ($n = 31$). Persistent pain was moderately correlated with pain-related disability, $r = .37$, $p < .001$, and highly correlated with pain intensity, $r = .54$, $p < .001$. Pain intensity was also highly correlated with pain-related disability, $r = .59$, $p < .001$. The presence of moderate-to-high correlations between pain characteristics could indicate issues with multicollinearity if all three variables are included in the same statistical model (Grewal, Cote, & Baumgartner, 2004).

As expected, the nicotine deprivation manipulation check revealed that deprived participants ($n = 62$; 51.6% female) had significantly lower levels of expired CO ($M = 5.31$, $SD = 2.11$) than nondeprived participants ($n = 58$; 51.7% female; expired CO $M = 38.74$, $SD = 21.13$; $p < .001$). Cigarette dependence (FTCD scores) and cessation self-efficacy were found to differ as a function of the deprivation condition. Participants in the deprived condition endorsed lower levels of cigarette dependence ($M = 5.39$, $SD = 1.86$) and greater cessation self-efficacy ($M = 1.11$, $SD = 1.17$) than participants in the nondeprived condition (FTCD: $M = 6.14$, $SD = 1.78$; cessation self-efficacy: $M = .62$, $SD = .61$; $p < .05$). There were no differences in any other sociodemographic variable, pain characteristic, or smoking characteristic as a function of deprivation condition assignment. Significant correlations were observed between gender and MNWS scores, $r = .20$, $p = .028$, and gender and number of cigarettes smoked during the laboratory paradigm, $r = -.21$, $p = .019$. Specifically, women had higher MNWS scores ($M = 2.27$, $SD = .84$) than men ($M = 1.93$, $SD = .85$). In comparison, men smoked a greater number of cigarettes ($M = 3.31$, $SD = 1.26$) than women ($M = 2.77$, $SD = 1.20$). Thus, cigarette dependence, cessation self-efficacy, and gender were included as covariates in subsequent analyses.

Nicotine Withdrawal

All ANCOVA models examining withdrawal outcomes are presented in Table 2. Associations between the three interaction terms

Table 1
Sociodemographic, Smoking, and Pain Characteristics

		Pain persistence		Pain intensity		Pain-related disability	
Demographic	Total sample	No persistent pain	Persistent pain	None-to-low	High	None-to-low	Moderate-to-severe
Gender							
Male	58 (48.3%)	44 (49.4%)	14 (45.2%)	38 (52.1%)	20 (42.6%)	47 (52.8%)	11 (35.5%)
Race							
White	90 (75.0%)	62 (69.7%)	28 (90.3%)	55 (75.3%)	35 (74.5%)	65 (73.0%)	25 (80.6%)
Non-White	30 (25.0%)	27 (30.3%)	3 (9.7%)	18 (24.7%)	12 (25.5%)	24 (27.0%)	6 (19.4%)
Marital status							
Single	71 (59.2%)	53 (59.6%)	18 (58.1%)	44 (60.3%)	27 (57.4%)	55 (61.8%)	16 (51.6%)
Married	18 (15.0%)	14 (15.7%)	4 (12.9%)	11 (15.1%)	7 (14.9%)	11 (12.4%)	7 (22.6%)
Separated, divorced, or widowed	21 (25.8%)	22 (24.7%)	9 (29.0%)	18 (24.7%)	13 (27.7%)	23 (25.8%)	8 (25.8%)
Education							
Did not graduate high school	21 (17.5%)	19 (21.3%)	2 (6.5%)	13 (17.8%)	8 (17.0%)	16 (180.0%)	5 (16.1%)
High school graduate	38 (31.7%)	27 (30.3%)	11 (35.5%)	24 (32.9%)	14 (29.8%)	25 (28.1%)	13 (41.9%)
Some college or greater	61 (50.8%)	43 (48.3%)	18 (58.0%)	36 (49.3%)	25 (53.2%)	48 (53.9%)	13 (42%)
Annual income							
<$10,000	53 (44.2%)	40 (44.9%)	13 (41.9%)	30 (41.1%)	23 (48.9%)	38 (42.7%)	15 (48.4%)
$10,000–$30,000	40 (33.3%)	27 (30.3%)	13 (41.9%)	21 (28.8%)	19 (40.4%)	26 (29.2%)	14 (45.2%)
>$30,000	27 (22.5%)	22 (24.7%)	5 (16.1%)	22 (30.1%)	5 (10.6%)	25 (28.1%)	2 (6.5%)
Age, *M* (*SD*)	36.17 (12.16)	36.36 (11.98)	35.64 (12.86)	34.68 (12.35)	38.50 (11.61)	35.51 (12.46)	38.06 (11.24)
Cigarettes per day, *M* (*SD*)	20.51 (6.99)	20.54 (7.36)	20.43 (5.90)	20.50 (6.43)	20.52 (7.85)	20.12 (6.20)	21.62 (8.90)
Years of smoking, *M* (*SD*)	16.77 (10.94)	17.37 (11.26)	15.06 (9.96)	15.37 (10.90)	18.96 (10.76)	15.68 (10.56)	19.90 (11.58)
FTCD, *M* (*SD*)	5.75 (1.85)	5.71 (1.80)	5.87 (2.03)	5.61 (1.80)	5.95 (1.93)	5.66 (1.81)	6.00 (1.96)
Cessation self-efficacy, *M* (*SD*)	.88 (.98)	.88 (.98)	.85 (.99)	.83 (.96)	.95 (1.01)	.84 (.98)	.97 (.97)
Expired carbon monoxide, *M* (*SD*)	21.47 (22.31)	21.46 (23.43)	21.48 (19.05)	21.08 (24.90)	22.06 (17.80)	21.92 (23.74)	20.16 (17.85)

Note. FTCD = Fagerström Test for Cigarette Dependence. Data are presented as *n* (%) unless otherwise noted.

Table 2
Pain Characteristics and Nicotine Deprivation as Predictors of Nicotine Withdrawal Reporting

Predictors	*df*	*F*	*p*	η_p^2
Persistent pain				
FTCD		2.685	.104	.023
Gender	1	5.540	.020*	.046
Cessation self-efficacy	1	1.328	.252	.012
Nicotine deprivation	1	9.917	.002**	.080
Persistent pain	1	7.100	.009**	.059
Pain intensity				
FTCD	1	2.375	.126	.020
Gender	1	5.119	.026*	.043
Cessation self-efficacy	1	1.653	.201	.014
Nicotine deprivation	1	9.788	.002**	.079
Pain intensity	1	2.627	.108	.023
Pain-related disability				
FTCD	1	2.534	.114	.022
Gender	1	5.100	.026*	.043
Cessation self-efficacy	1	1.332	.251	.012
Nicotine deprivation	1	8.485	.004**	.069
Pain-related disability	1	0.489	.486	.004

Note. FTCD = Fagerström Test for Cigarette Dependence.
* $p < .05$. ** $p < .01$.

(i.e., deprivation x persistent pain, deprivation x pain intensity, deprivation x pain-related disability) and nicotine withdrawal severity were all not statistically significant. Therefore, we interpreted the main effects at the second step of each model (Huitema, 2011). As expected (Heckman et al., 2017), nicotine-deprived participants reported more severe withdrawal (M = 2.27, SD = .82) than nondeprived participants (M = 1.92, SD = .86; ps < .05). There was no difference in withdrawal reporting as a function of pain intensity, $F(1, 120) = 2.62$; $p = .108$ or pain-related disability, $F(1, 120) = .489$; $p = .486$. Participants with persistent pain reported experiencing more severe withdrawal (M = 2.43, SE = .14), relative to those with no persistent pain (M = 1.98, SE = .09), $F(1, 120) = 7.10$; $p = .009$; $\eta_p^2 = .059$.

Laboratory Smoking Cessation Outcomes

Lapse. Across the entire sample, the mean time to smoking the first cigarette (i.e., lapse) was approximately 20 min (SD = 20.34). No significant interactions between nicotine deprivation condition and either persistent pain, pain intensity, or pain-related disability on lapse behavior were observed (ps > .05). Consistent with the primary study, nicotine deprivation increased the likelihood of lapse behavior ($p < .05$; Table 3). Pain-related disability was also a predictor of latency to lapse (hazard ratio [HR] = 1.93, $p = .014$; see Table 3), such that participants with moderate-to-severe (vs. none-to-low) pain-related disability were at almost twice the risk of initiating smoking. Kaplan Meier survival analysis further indicated that the presence of moderate-to-severe pain related disability predicted a more rapid trajectory to initiating smoking ($p = .029$; Figure 1). Neither persistent pain (HR = 1.45, $p = .176$) nor pain intensity (HR = 1.61, $p = .063$) predicted lapse behavior, and no statistically significant differences in lapse trajectories were observed as a function of persistence or intensity (ps > .05).

Relapse. On average, participants smoked 3 cigarettes (SD = 1.26) during the ad lib smoking period. There were no significant interactions between nicotine deprivation and either persistent pain, $F(1, 120) = .97$; $p = .326$, pain intensity, $F(1, 120) = .41$ $p = .520$, or pain-related disability, $F(1, 120) = .01$; $p = .905$, on the relapse outcome. There was also no main effect of deprivation on number of cigarettes smoked in any model. Similarly, there was no effect of persistent pain, $F(1, 120) = .01$; $p = .964$, pain intensity, $F(1, 120) = 1.34$; $p = .249$, or pain-related disability, $F(1, 120) = .07$; $p = .791$, on the relapse outcome.

Discussion

This is the first study to examine clinically relevant pain characteristics (i.e., pain persistence, intensity, and disability) as predictors of nicotine withdrawal and cessation-relevant outcomes. Lapse and relapse behavior was assessed using a laboratory paradigm of smoking cessation. Results indicated that smokers with persistent pain (vs. no persistent pain) scored higher on a measure of nicotine withdrawal prior to completing the laboratory paradigm, regardless of deprivation condition assignment. Examination of the partial eta squared values revealed that the effect of persistent pain on nicotine withdrawal may be characterized as small-to-moderate in magnitude. Results also indicated that smokers with moderate-to-severe levels of pain-related disability initiated smoking (i.e., lapse behavior) faster than smokers with none-to-low levels of pain-related disability. Importantly, these effects were evident above and beyond the variance accounted for by cigarette dependence, cessation self-efficacy, gender, nicotine de-

Table 3
Cox Proportional Hazards Regressions Examining Minutes to First Cigarette (i.e., Lapse) During the Laboratory Paradigm of Smoking Cessation

Predictors	Adjusted hazard ratio	95% CI	*p*
Persistent pain			
FTCD	0.965	[0.840, 1.108]	.612
Gender	0.784	[0.479, 1.285]	.335
Cessation self-efficacy	0.753	[0.560, 1.012]	.060
Self-control depletion	1.711	[1.029, 2.845]	.038*
Nicotine deprivation	1.628	[0.974, 2.720]	.063
Persistent pain	1.447	[0.848, 2.472]	.176
Pain intensity			
FTCD	0.963	[0.839, 1.106]	.596
Gender	0.798	[0.487, 1.306]	.369
Cessation self-efficacy	0.728	[0.538, .984]	.039*
Self-control depletion	1.759	[1.053, 2.938]	.031*
Nicotine deprivation	1.681	[1.003, 2.818]	.049*
Pain intensity	1.610	[0.975, 2.659]	.063
Pain-related disability			
FTCD	0.953	[0.831, 1.094]	.497
Gender	0.739	[0.447, 1.221]	.237
Cessation self-efficacy	0.747	[0.556, 1.005]	.054
Self-control depletion	1.683	[1.008, 2.808]	.046*
Nicotine deprivation	1.543	[0.926, 2.571]	.096
Pain-related disability	1.926	[1.139, 3.258]	.014*

Note. FTCD = Fagerström Test for Cigarette Dependence. Indicator groups for categorical variables: gender (female), self-control depletion (not depleted), nicotine deprivation (not deprived), pain (no pain).
* $p < .05$.

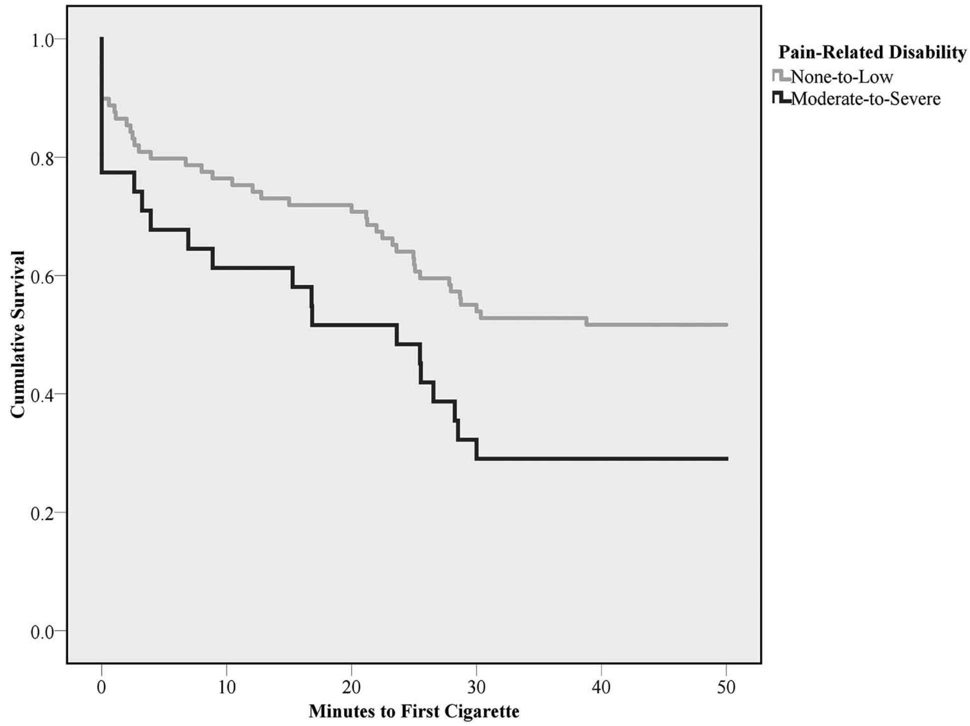

Figure 1. Kaplan–Meier survival curves of minutes to first cigarette (i.e., lapse) during the laboratory paradigm as a function of pain-related disability.

privation condition, and the self-control depletion manipulation. Although nicotine deprivation predicted both greater withdrawal severity and increased lapse behavior, we observed no interaction between deprivation condition and either persistent pain or pain-related disability on these outcomes. We also observed no main effect of either deprivation condition or pain characteristics on number of cigarettes smoked (i.e., relapse behavior) during the experimental paradigm.

This study advances prior work documenting that smokers with pain (vs. no pain) tend to experience greater difficulty quitting (Zale et al., 2014) and anticipate more severe nicotine withdrawal when attempting to quit smoking (Ditre, Kosiba, et al., 2016). Laboratory studies have shown that some withdrawal symptoms emerge within 30 min of finishing a cigarette (Hendricks, Ditre, Drobes, & Brandon, 2006), and there has been interest in examining fluctuations in withdrawal reporting among continued smokers (Chandra, Scharf, & Shiffman, 2011; Perkins, Briski, Fonte, Scott, & Lerman, 2009). In fact, greater withdrawal severity among current non-treatment-seeking smokers has been shown to predict decreased odds of reducing smoking and initiating future quit attempts (Weinberger, Desai, & McKee, 2010; Weinberger, Platt, Shuter, & Goodwin, 2016). The finding that smokers with persistent pain reported more severe withdrawal, regardless of deprivation condition assignment, suggests these individuals may be less likely to successfully quit smoking, relative to smokers without persistent pain. Additionally, these findings suggest that pain persistence may differentially predict greater nicotine withdrawal compared to pain intensity and pain-related disability. Given the preliminary nature of these findings, future work is needed to examine changes in withdrawal reporting among both smokers and recent quitters as a function of pain characteristics.

The current results also indicated that participants with moderate-to-severe pain-related disability (vs. none-to-low pain-related disability) were almost twice as likely to initiate smoking (and smoked their first cigarette faster) during the laboratory paradigm of smoking cessation. In contrast, neither pain persistence nor pain intensity predicted lapse behavior. Our finding that smokers with moderate-to-severe pain-related disability initiated smoking faster during the experimental paradigm is consistent with a growing literature suggesting that pain may play an important role in lapse/relapse to smoking (Aigner et al., 2017; LaRowe et al., 2017; Nakajima & al'Absi, 2011), and that pain-related disability may confer unique predictive utility (i.e., beyond pain status or intensity) in the prediction of substance-related outcomes (e.g., Zale & Ditre, 2015; Zale, Lange, Fields, & Ditre, 2013). For example, greater fear of pain has been associated with greater pain-related disability and the worsening of pain over time (Crombez, Vlaeyen, Heuts, & Lysens, 1999; Vlaeyen & Linton, 2000), and it has been hypothesized that smokers with elevated pain-related fear/disability may be more likely to use tobacco to self-medicate pain symptoms (LaRowe, Zvolensky, & Ditre, 2018). In addition, smokers tend to endorse higher levels of pain-related disability than nonsmokers (Hooten et al., 2011; Patterson et al., 2012), and chronic pain patients who score higher on measures of pain-related disability are more likely to report using cigarettes for pain-coping (Patterson et al., 2012). Contrary to expectation, we observed no effect of pain persistence or pain intensity on experimental lapse outcomes. Collectively, these findings suggest that pain-related disability may uniquely predict likelihood of lapse to smoking; however, additional work is needed to replicate these findings and further establish the predictive utility of pain-related disability relative to other pain characteristics, in the context of prospective smoking cessation studies.

Strengths of the current study include its rigorous experimental design, and use of reliable and valid measures of pain, cigarette dependence, and smoking withdrawal. Several limitations also bear noting. First, participants were not recruited based on the presence of pain, and these findings should be replicated among larger samples with varying levels and sources of pain. Nonetheless, the high prevalence of pain in the current sample (e.g., approximately 40% endorsed high pain intensity) is consistent with prevalence data (Bakhshaie et al., 2016), indicating good representativeness, and supports the utility of assessing pain among all smokers, regardless of chronic pain status. Second, the sample was comprised of heavy smokers who smoked at least 15 cigarettes per day and were not currently attempting to quit. Thus, the extent to which these results may generalize to lighter smokers, treatment-seeking smokers, or smokers who are actively attempting to quit remains unclear. An important next step in this line of work would be to test pain characteristics in the prediction of withdrawal and established cessation milestones among individuals who are actively attempting to quit smoking (i.e., initial abstinence, lapse, relapse; Shiffman et al., 2006). A follow-up period of at least 2 weeks has been suggested for cessation research (Baker et al., 2011), as initial smoking lapses are most likely to occur during this timeframe (Garvey, Bliss, Hitchcock, Heinold, & Rosner, 1992; Hughes, Keely, & Naud, 2004). Third, nicotine withdrawal severity was not controlled for when examining lapse and relapse, and it is possible that greater withdrawal may have accounted for variance in these outcomes. Additional work is needed to determine the extent to which differences in the experience of withdrawal may contribute to smoking cessation outcomes among smokers with pain. Fourth, lapse and relapse outcomes were assessed using a validated laboratory model of smoking cessation (McKee, 2009; McKee et al., 2012). Whereas this approach enhances internal validity (e.g., Leeman et al., 2010; Leventhal et al., 2014), external validity is inherently limited as these data do not necessarily reflect 'real-world' lapse or relapse processes. Fifth, although expired CO of $\leq$11 ppm has been used to verify 12-hr smoking abstinence (e.g., Leventhal et al., 2010; Roche et al., 2014; Wilson et al., 2014), future research may benefit from employing more stringent cut-offs to reduce the likelihood of Type II error (Cropsey et al., 2014). Sixth, given that deprived participants were required to remain abstinent for 12 hr, smokers with greater cigarette dependence or less motivation to quit may have been underrepresented in the deprivation condition. Although cigarette dependence, cessation self-efficacy, and deprivation assignment were controlled for statistically in the current study, future work may address this concern through within-subject designs. Finally, although we observed no effect of any pain characteristic on the relapse outcome (i.e., number of cigarettes smoked), it is common for factors that predict lapse behavior do not also predict relapse behavior (and vice versa) in the experimental cessation paradigm (Langdon & Leventhal, 2014; Leventhal et al., 2014; Pang & Leventhal, 2013; Reitzel & Leventhal, 2014; Roche et al., 2014). For example, Roche and colleagues (2014) found that only 2 of 11 established risk factors (withdrawal and craving to relieve the discomfort of withdrawal) predicted both latency and number of cigarettes smoked. Collectively, these findings suggest that the laboratory paradigm provides distinct indices of lapse and relapse processes, and that smokers with pain-related disability may be more sensitive to lapses.

A growing body of evidence indicates that pain is linked to smoking behavior and the maintenance of tobacco dependence, and these data contribute to an emerging literature indicating that smokers with pain are at risk for poorer cessation outcomes. In the current study, persistent pain and pain-related disability independently predicted greater nicotine withdrawal and lapse behavior. Thus, it may be beneficial to incorporate assessment of clinically relevant pain characteristics among smokers who are preparing to quit. There is evidence that smokers with pain (vs. no pain) are more likely to seek out pharmacotherapy for cessation (Zale & Ditre, 2014), and it has been suggested that these individuals may benefit from high-dose or combination nicotine replacement therapy (Hatsukami et al., 2007; Mills et al., 2012; Zale & Ditre, 2014). Behavioral cessation interventions have also been successfully administered to smokers with chronic pain (Saragiotto et al., 2018), and integrated treatments for pain and smoking have been shown to increase knowledge of pain-smoking interrelations, and confidence/intention to quit smoking (Ditre, LaRowe, Vanable, De Vita, & Zvolensky, 2019; Hooten, LaRowe, Zale, Ditre, & Warner, 2019).

In summary, this is the first study to test clinically relevant pain characteristics as predictors of withdrawal reporting and smoking lapse/relapse behavior. These findings suggest that pain persistence and pain-related disability may predict different cessation outcomes (i.e., nicotine withdrawal, and early lapse to smoking). Limited research has examined the effects of pain in smoking cessation, and these findings represent an initial, yet important step toward better understanding the role of pain characteristics in the maintenance of tobacco dependence. This and future work has the potential to inform the development of integrated treatments, including relapse-prevention interventions (e.g., Meltzer et al., 2018) for smokers with co-occurring pain.

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