



Relations between pain-related anxiety, tobacco dependence, and barriers to quitting among a community-based sample of daily smokers



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HIGHLIGHTS

- 17% of 122 daily smokers endorsed moderate to severe past-month pain.
- Pain-related anxiety was associated with tobacco dependence and barriers to quitting.
- These data underscore the importance of assessing pain among all smokers.
- Covariation between pain, pain-related anxiety, and smoking may impede quitting.

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ABSTRACT

There is increasing recognition that complex and potentially bidirectional relations between pain and smoking may be relevant to the maintenance of tobacco addiction. Pain-related anxiety has been identified as a mechanism in the onset and progression of painful disorders, and initial evidence indicates that pain-related anxiety may be associated with essential features of tobacco dependence among smokers with chronic pain. However, there has not been an empirical study of pain-related anxiety in relation to tobacco dependence and self-reported barriers to quitting among a community-based sample of daily smokers. The current sample was comprised of 122 daily smokers who were recruited from the local community to participate in a larger study that included an initial assessment of pain, smoking history, and pain-related anxiety. Approximately 17% of our sample endorsed moderate or severe past-month pain, nearly half met criteria for current anxiety or mood disorder, and about 30% met criteria for a current substance use disorder, exclusive of tobacco dependence. Results indicated that pain-related anxiety was uniquely and positively associated with both tobacco dependence severity scores and self-reported barriers to quitting. These findings lend support to the notion that pain-related anxiety may contribute to the maintenance of tobacco addiction among smokers who experience varying levels of pain severity.

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1. Introduction

Pain and tobacco smoking are both highly prevalent and comorbid conditions, and accumulating research indicates that relations between pain and smoking are likely complex and bidirectional in nature (Ditre, Brandon, Zale, & Meagher, 2011; Parkerson, Zvolensky, & Asmundson, 2013). For example, pain has been shown to be a potent motivator of smoking (Ditre & Brandon, 2008; Ditre, Heckman, Butts, & Brandon, 2010); smoking has been identified as a unique causal factor in the onset and exacerbation of painful conditions (e.g., Sugiyama et al.,

2010); and, there is evidence that pain may pose a significant barrier to smoking cessation (Zale & Ditre, 2013; Zale, Ditre, Dorfman, Heckman, & Brandon, 2014). To better inform the development of tailored cessation interventions for smokers in pain, researchers have recently turned their attention to the identification of mechanistic factors in the etiology, progression, and maintenance of comorbid pain and tobacco smoking. One factor that appears to be of theoretical and clinical importance is the cognitive–affective construct termed *pain-related anxiety*.

Pain-related anxiety reflects the tendency of an individual to respond with anxiety or fear to actual or potential pain experiences (McCracken, Zayfert, & Gross, 1992). Pain-related anxiety has been described as closely related to, but empirically and theoretically distinct from, other cognitive–affective constructs that tend to be encompassed

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by the higher-order construct of pain-related fear, including fear of activities that may elicit pain (Lundberg, Grimby-Ekman, Verbunt, & Simmonds, 2011; Zale, Lange, Fields, & Ditre, 2013). Pain-related anxiety is a risk factor in the transition from acute to chronic pain (Boersma & Linton, 2006; Vlaeyen & Linton, 2000), and greater pain-related anxiety has been related to overestimated appraisals of pain intensity, maladaptive approaches to pain coping, and increased somatic reactivity in anticipation of pain-eliciting physical activity (McCracken, Gross, Sorg, & Edmands, 1993).

More recently, pain-related anxiety has been implicated in the maintenance of substance use in general (Hogan, Gonzalez, Howell, Bonn-Miller, & Zvolensky, 2010), and tobacco smoking in particular (Ditre, Zale, Kosiba, & Zvolensky, 2013; Gonzalez, Hogan, McLeish, & Zvolensky, 2010). For example, among a sample of daily smokers who endorsed recent body pain, pain-related anxiety was found to be positively associated with expectancies that smoking decreases negative affect (Gonzalez et al., 2010). In addition, and of direct relevance to the current study, pain-related anxiety was also observed to be uniquely and positively associated with tobacco dependence severity scores among a sample of daily smokers with chronic pain (Ditre et al., 2013). It is important to note that the associations observed in each of these studies remained significant even after accounting for a host of potential third variables, including, gender, pain intensity, smoking rate, and variance shared with related cognitive–affective constructs (e.g., generalized anxiety, anxiety sensitivity). Thus, pain-related anxiety may be uniquely related to tobacco dependence.

A growing body of empirical evidence suggests that pain and pain-related constructs are relevant to all smokers regardless of chronic pain status (e.g., Ditre & Brandon, 2008; Ditre et al., 2010; Zale et al., 2014). Considering that pain-related anxiety has been associated with tobacco dependence among smokers with chronic pain, an important next step in this line of research is to assess the extent to which pain-related anxiety may be associated with tobacco dependence among smokers recruited from the local community (i.e., those not specifically recruited for positive chronic pain status). There is evidence to suggest that smokers in pain may face unique challenges to smoking cessation (e.g., Hooten et al., 2011) and have limited confidence in their ability to successfully quit smoking (Zale et al., 2014). However, little is known about how cognitive–affective pain processes (e.g., pain-related anxiety) may be associated with perceived barriers to smoking cessation.

Accordingly, the goal of the present study was to test cross-sectional relations between pain-related anxiety, tobacco dependence severity scores, and self-reported barriers to quitting, among a community-based sample of daily smokers with varying levels of pain. Specifically, we hypothesized that greater pain-related anxiety would be associated with higher scores on a comprehensive, theoretically grounded, multidimensional measure of tobacco dependence (Wisconsin Inventory of Smoking Dependence Motives; Piper et al., 2004). We also hypothesized that greater pain-related anxiety would be associated with a greater number and magnitude of self-reported barriers to smoking cessation. Finally, we predicted that these relations would remain significant after controlling for relevant sociodemographic factors, current pain severity, and the presence of comorbid anxiety, mood, or substance use disorders.

2. Method

2.1. Participants

Participants were recruited from the local community via flyers and newspaper advertisements for a larger smoking study that required a self-guided quit attempt. Interested participants were screened by phone for age (18–65), endorsement of current smoking (8 or more cigarettes per day for a minimum of one year), and willingness to make a self-guided quit attempt. Participants were excluded from the

study if they endorsed current use of nicotine replacement or other tobacco products, current or past history of psychotic-spectrum symptoms or disorders, current substance dependence (excluding nicotine dependence), and current use of psychotropic medication. Eligible participants were scheduled for a baseline visit at which time they provided written, informed consent and smoking status was biochemically verified via expired breath Co (≥ 8 ppm). Interviewer and self-report data utilized in the current analyses were collected during this baseline assessment visit prior to the self-guided quit attempt.

2.2. Measures

2.2.1. Pain-related anxiety

The Pain-Anxiety Symptoms Scale–20 item (PASS-20; McCracken & Dhingra, 2002) is a measure of anxious or fearful responses to pain, with higher total scores indicative of greater pain-related anxiety. Factor-analytic methods support a four-factor structure comprised of (1) escape/avoidance behaviors when confronted with pain, (2) physical anxiety associated with pain, (3) cognitive/affective anxiety associated with pain, and (4) fear of experiencing pain. The PASS-20 has demonstrated adequate reliability and validity in nonclinical samples (Abrams, Carleton, & Asmundson, 2007; McCracken & Dhingra, 2002), and internal consistency of the total score in the current sample was excellent (Cronbach's $\alpha = .91$). The internal consistency of the subscales was good (range of Cronbach's $\alpha = .75–.86$).

2.2.2. Recent bodily pain

The Short Form Health Survey–20 (SF-20; Stewart & Ware, 1992) is a 20 item self-report measure of general mental and physical health. Consistent with previous research, a single item was used to assess the presence of past-month bodily pain (i.e., “How much bodily pain have you had during the past four weeks”; Ware, Kosinski, & Gandek, 2000). Response options ranged from 1 (*None*) to 5 (*Severe*).

2.2.3. Tobacco dependence

The Wisconsin Inventory of Smoking Dependence Motives (WISDM; Piper et al., 2004) is a 68-item, multidimensional index of tobacco dependence that yields a total dependence score (WISDM-Total), which is comprised of two composite scores (Primary Dependence Motives–PDM, and Secondary Dependence Motives–SDM). The WISDM assesses a broad range of dependence constructs, which allows for detection of theoretically- and clinically-meaningful distinctions among smokers (Piper et al., 2008). The PDM composite score is composed of four subscales that assess central features of tobacco dependence, whereas the SDM composite is comprised of nine subscales that assess situational motivators of smoking. The WISDM is a reliable and valid measure of tobacco dependence that demonstrated excellent internal consistency in the current sample across the total score and subscales (range of Cronbach's $\alpha = .91–.97$).

2.2.4. Self-reported barriers to smoking cessation

The Barriers to Cessation Scale (BCS; Macnee & Talsma, 1995) is a 19-item measure that assesses the severity of perceived difficulties associated with making a successful cessation attempt (e.g., withdrawal, lack of social support, feeling less in control of moods). Items are rated on a Likert-type scale from (0 = *Not a barrier/not applicable* to 3 = *Large barrier*). Consistent with prior work, we utilized the total score (Peasley-Miklus, McLeish, Schmidt, & Zvolensky, 2012), with higher total scores indicative of a greater number and magnitude of anticipated barriers to quitting. This measure has demonstrated good content validity, predictive validity and internal consistency (Macnee & Talsma, 1995). The internal consistency in the current sample was good (Cronbach's $\alpha = .87$).

Table 1
Sample demographic and clinical characteristics.

Participant characteristics (N = 122)		
	N	%
Gender		
Female	42	34.4
Education**		
Did not graduate high school	4	3.3
High school or part college	85	69.7
Technical school/Associates	7	5.7
Four-year college	15	12.3
Some school beyond college	8	6.6
Ethnicity**		
Hispanic/Latino	5	4.1
Not Hispanic/Latino	114	93.4
Race		
Caucasian	97	79.5
Black/African American	11	9.0
Other	14	11.0
SCID-IV-N/P results ^a		
Current anxiety disorder	41	33.6
Current mood disorder	15	12.3
Current substance use disorder	35	28.7
Pain intensity ^{b*}		
None	25	20.5
Very mild	41	33.6
Mild	22	18.0
Moderate	17	13.9
Severe	4	3.3
	M	SD
Age	33.5	13.6
FTND ^c	3.5	1.9
Cigarettes per day	15.7	6.3
PASS ^d -20 Total	30	18
PASS-20 Cognitive anxiety	8.9	5.9
PASS-20 Escape/avoidance	9.0	5.4
PASS-20 Fear	5.9	5.3
PASS-20 Physical anxiety	6.3	5.0
WISDM-Total ^e	53.4	14.8
WISDM-PDM	4.4	1.3
WISDM-SDM	4.0	1.2
BCS-Total ^f	25.4	9.7

^a Structured Clinical Interview for DSM-IV Non-Patient Edition (SCID-IV-N/P).

^b Short Form Health Survey–20.

^c Fagerstrom Test for Nicotine Dependence.

^d Pain Anxiety Symptoms Scale.

^e Wisconsin Inventory of Smoking Dependence.

^f Barriers to Cessation–Total Score (BCS). *13 participants did not provide data.

**3 participants did not provide data.

2.2.5. Current anxiety, mood and substance use disorders

All participants were administered the Structured Clinical Interview for DSM-IV-TR Axis I Disorders, Non-Patient Edition (SCID-IV-N/P; Michael et al., 2002). Disorders were considered current if the participant met diagnostic criteria at the time of the baseline visit. Diagnostic outcomes were then dichotomized (0 = negative, 1 = positive) to reflect current disorder status. All SCID-N/P interviews were audio-taped and the reliability of a random selection of 10% of interviews was checked for accuracy. No diagnostic disagreements were observed between the SCID interviewer and the outside rater.

2.2.6. Tobacco smoking

Historical and current tobacco use (e.g., smoking status, number of cigarettes smoked per day) were assessed via self-report and are presented in Table 1. Participants also completed the Fagerström Test for Nicotine Dependence (FTND; Heatherton, Kozlowski, Frecker, & Fagerström, 1991), which is a widely-used measure of nicotine dependence.

2.3. Data analytic strategy

We first ran a series of bivariate correlations to test zero-order associations between scores on the PASS-20, pain severity, presence of current anxiety, mood, or substance use disorders, and sociodemographic characteristics. Bivariate relationships showed that PASS-20 scores were positively associated with male gender ($r = .29$), current anxiety disorder status ($r = .47$), and pain severity ($r = .29$; all $ps < .04$). These variables were retained as covariates in the regression models. Neither current mood disorder status nor substance use disorder status was associated with PASS-20 scores ($ps > .11$). However, these variables were retained in the model due to previously observed relations with both pain and tobacco smoking (Ditre et al., 2011). We then conducted separate hierarchical regressions to test the a priori hypotheses that pain-related anxiety (i.e., PASS-20 Total scores) would be positively associated with tobacco dependence (i.e., WISDM-Total scores) and self-reported barriers to smoking cessation (i.e., BCS-Total scores). For each of the regression models, predictors were entered in the following order: Step 1 (gender, presence of current anxiety, mood, or substance use disorders, pain severity); Step 2 (pain-related anxiety). We assessed the relative contribution of pain-related anxiety to the observed variance in our measures of smoking dependence and self-reported barriers to quitting by examining change in R-squared (ΔR^2) at the second step of each model. Similar analyses were conducted to explore associations between PASS-20 subscale scores, WISDM PDM and SDM composite scores, and BCS-Total scores.

3. Results

3.1. Sample characteristics

The sample included 122 daily smokers (64.5% male; $M_{\text{age}} = 33.5$; $SD = 13.6$), who reported smoking an average of 16 cigarettes per day ($SD = 6.3$) for approximately 16 years ($SD = 13$). The mean FTND score was 3.5 ($SD = 1.9$), indicating a low-to-moderate level of nicotine dependence (Heatherton et al., 1991). Approximately 79% of the sample endorsed having experienced at least *very mild* pain over the past 4 weeks, and about 17% endorsed *moderate* or *severe* pain. Structured clinical interviews (SCID-IV-N/P) revealed that just over half the sample (52%) met criteria for more than one anxiety, mood, or substance use disorder. Among those with a current substance use disorder, 13% met criteria for substance abuse and 27% met criteria for substance dependence, with the most common being marijuana dependence (10.7%) and alcohol dependence (10.7%). Among those with a current anxiety or mood disorder, social phobia (13.9%) and major depression (6.6%) were the most common. Additional sociodemographic and clinical data are presented in Table 1.

3.2. Pain-related anxiety and tobacco dependence

As hypothesized, results indicated that greater levels of pain-related anxiety were associated with higher scores on a comprehensive measure of tobacco dependence. Specifically, examination of ΔR^2 indicated that, after accounting for the influence of gender, pain, and presence of current anxiety, mood, or substance use disorders, scores on the PASS-20 explained about 6% of the unique variance in observed WISDM-Total scores ($p = .01$), 5% of the variance in WISDM PDM scores ($p = .03$), and 5% of the variance in WISDM SDM scores ($p = .02$). As seen in Table 2, exploratory analyses revealed similar associations between greater scores on each of the Fear, Cognitive/Affective, and Physical Anxiety subscales of the PASS-20 and greater WISDM-Total scores (all $ps < .04$). PASS-20 scores were not related to FTND scores.

Table 2

Associations between PASS-20 Total scores and WISDM subscale scores at the final step of each hierarchical model.

	PASS-20 ^a Total score			
	β	<i>t</i>	ΔR^2	<i>p</i>
Criterion variables:				
WISDM ^b Primary Dependence Motives Subscales				
Automaticity	.29	2.63	.06	.01*
Craving	.27	2.43	.05	.02*
Loss of control	.26	2.33	.05	.02*
Tolerance	-.01	-.05	.00	.96
WISDM ^b Secondary Dependence Motives Subscales				
Affiliative attachment	.34	3.09	.08	<.01**
Behavioral choice/melioration	.29	2.63	.06	.01*
Cognitive enhancement	.14	1.20	.01	.23
Cue exposure/associative processes	.16	1.42	.02	.16
Negative reinforcement	.25	2.17	.04	.03*
Positive reinforcement	.27	2.43	.05	.02*
Social/environmental goals	.14	1.23	.01	.22
Taste/sensory properties	.07	.57	.00	.57
Weight control	.18	1.70	.02	.09

These data reflect step three of the individual hierarchical regressions of pain-related anxiety (PASS-20 Total) on WISDM subscale scores. Thus, all analyses adjusted for gender, pain severity, and anxiety/mood/substance use disorder status. β = standardized beta weights.

^a Pain Anxiety Symptoms Scale-20.

^b Wisconsin Inventory of Smoking Dependence Motives.

* $p < .05$.

** $p < .01$.

3.3. Pain-related anxiety and barriers to smoking cessation

Also as hypothesized, results indicated that greater levels of pain-related anxiety were associated with a greater number and magnitude of self-reported barriers to smoking cessation. Specifically, examination of ΔR^2 values indicated that, after accounting for the influence of gender, pain severity, and presence of current anxiety, mood, or substance use disorders, scores on the PASS-20 explained about 9% of the unique variance in observed BCS scores ($p < .01$). As seen in Table 3, exploratory analyses revealed similar positive associations between greater scores on each of the Escape/Avoidance, Cognitive/Affective, and Physical Anxiety subscales of the PASS-20 and the BCS-Total score (all $ps < .01$).

4. Discussion

To our knowledge, this is the first study to test associations between pain-related anxiety, smoking dependence motives, and self-reported

barriers to quitting among smokers recruited from a community sample. As hypothesized, pain-related anxiety was observed to be significantly and positively associated with both tobacco dependence severity scores and the number/magnitude of perceived barriers to smoking cessation. Importantly, these associations remained significant even after accounting for the influence of gender, presence of current anxiety, mood, or substance use disorders, and pain severity. Exploratory analyses of individual PASS-20 subscale scores revealed a similar pattern of results.

Only recently have researchers begun evaluating pain-related, cognitive-affective processes as potential mechanisms in the maintenance of tobacco addiction (Ditre et al., 2011; Hooten, Shi, Gazelka, & Warner, 2011), and the current results are consistent with previous research demonstrating positive associations between pain-related anxiety and smoking dependence motives among persons with chronic pain (Ditre et al., 2013). However, pain-related anxiety was not related to FTND scores in these analyses. One possibility for these null findings could be that whereas the FTND predominantly measures physiological dependence on nicotine, the WISDM tends to be more sensitive to instrumental or situational smoking motivation (Piasecki, Piper, Baker, & Hunt-Carter, 2011; Shiffman, Dunbar, Scholl, & Tindle, 2012). In addition, we did not observe associations between the PASS Escape/Avoidance subscale (which assesses specific approaches to pain management such as “I go immediately to bed when I feel severe pain”) and the WISDM Total, PDM, or SDM scores. These results may reflect the tendency of nicotine dependent individuals to favor smoking in response to pain over alternative coping strategies (Ditre & Brandon, 2008).

These findings build upon previous work by providing novel evidence that greater pain-related anxiety may also be related to greater perceived barriers to quitting, among a more generalizable sample of smokers who were not recruited based on chronic pain status. Indeed, our finding that smokers with greater levels of pain-related anxiety scored higher on a measure of self-reported barriers to smoking cessation is in line with evidence that smokers in pain may experience greater difficulty and have less confidence in quitting (Zale et al., 2014). Results of the current study suggest that pain-related anxiety may be a worthy target for studies designed to test mechanisms underlying complex interrelations between pain, smoking, and cessation-relevant processes/outcomes.

It is also notable that, despite not recruiting based on pain status, approximately 79% of our sample of daily smokers reported having experienced at least some pain over the previous month. Specifically, 21% endorsed no pain, 34% endorsed very mild pain, 18% endorsed mild pain, and 17% endorsed moderate or severe pain. Such data are novel,

Table 3

Associations between PASS-20 scores, smoking dependence scores, and BCS scores at the final step of each hierarchical model.

	PASS-20 ^a Total score				PASS-20 Fear				PASS-20 Escape/avoidance				PASS-20 Cognitive/affective				PASS-20 Physical anxiety			
	β	<i>t</i>	ΔR^2	<i>p</i>	β	<i>t</i>	ΔR^2	<i>p</i>	β	<i>t</i>	ΔR^2	<i>p</i>	β	<i>t</i>	ΔR^2	<i>p</i>	β	<i>t</i>	ΔR^2	<i>p</i>
Criterion variables:																				
WISDM ^b																				
Total score ^c	.29	2.59	.06	.01*	.24	2.27	.05	.03*	.18	1.68	.03	.10	.24	2.20	.04	.03*	.24	2.13	.04	.04*
PDM ^d	.25	2.25	.05	.03*	.26	2.52	.06	.01*	.17	1.61	.02	.11	.14	1.23	.01	.22	.22	1.94	.03	.06
SDM ^e	.27	2.45	.05	.02*	.20	1.89	.03	.06	.16	1.52	.02	.13	.26	2.42	.05	.02*	.22	1.93	.04	.05
BCS ^f	.36	3.52	.09	<.01**	.17	1.67	.02	.10	.32	3.25	.08	<.01**	.32	3.22	.08	<.01**	.31	2.92	.07	<.01**
FTND ^g	.00	-.02	.00	.99	.01	.10	.00	.92	.00	.40	.00	.69	-.08	-.81	.01	.42	.04	.37	.00	.71

These data reflect step three of the individual hierarchical regressions of pain-related anxiety (PASS-20 Total and subscale scores) on WISDM and BCS scores. Thus, all analyses adjusted for gender, pain severity, and anxiety/mood/substance use disorder status. β = standardized beta weights.

^a Pain Anxiety Symptoms Scale-20.

^b Wisconsin Inventory of Smoking Dependence Motives.

^c WISDM-Total Score.

^d WISDM-Primary Dependence Motives.

^e WISDM-Secondary Dependence Motives.

^f Barriers to Cessation-Total Score (BCS).

^g Fagerstrom Test for Nicotine Dependence.

* $p < .05$.

** $p < .01$.

as we are aware of only one study that reported rates of past-month pain among smokers recruited from the general population (i.e., 59% in Zale et al., 2014), and one additional study that reported rates of “significant” past two-week pain among adult smokers in the control arm of a larger smoking cessation study (i.e., 28% in Hahn et al., 2006). Endorsement of pain in the current sample also exceeded rates observed in the general population (i.e., 51%; Barnes et al., 2008), which is consistent with evidence that smokers may be more likely than non-smokers to experience painful conditions (Ditre et al., 2011). Collectively, these data underscore the importance of assessing pain among all smokers, regardless of chronic pain status.

Several limitations are worth noting. First, the cross-sectional nature of these data precludes causal interpretations. Thus, the causal role of pain-related anxiety in relation to smoking dependence and barriers to cessation remains unclear. Second, the sample was comprised of participants who were willing to undertake a self-guided quit attempt, which may limit the generalizability of these findings. Third, although we accounted for relevant covariates, there may be other important factors (such as lifetime psychopathology or comorbid health disorders) that may increase the anxiety-eliciting properties of pain (Staats, Staats, & Hekmat, 2001; Thibodeau, Welch, Katz, & Asmundson, 2013). Fourth, only a single assessment of pain was utilized and we did not assess other factors (e.g., pain location) that may be related to both psychological functioning and variations in the pain experience (Miro, Gertz, Carter, & Jensen, 2014). Fifth, although we controlled for anxiety disorder status, we were not able to clarify the role of pain-related anxiety relative to other potentially relevant constructs, such as anxiety sensitivity (Carleton & Asmundson, 2009; Zvolensky, Goodie, McNeil, Sperry, & Sorrell, 2001). Finally, it should be noted that 13 participants did not provide pain data, and that Caucasian, non-Hispanic daily smokers were overrepresented in the current sample, thus limiting generalizability and our capacity to test potential moderating effects of race/ethnicity.

In summary, results of the current study represent an early, yet essential step towards better understanding potentially bidirectional relations between pain and tobacco smoking. Both pain and anxiety have been shown to independently motivate smoking behavior (Ditre & Brandon, 2008; Ditre et al., 2010; Jarvik, Caskey, Rose, Herskovic, & Sadehghpour, 1989), and several studies have documented positive relations between anxiety-related cognitive processes and perceived barriers to quitting (Gonzalez, Zvolensky, Vujanovic, Leyro, & Marshall, 2008; Gregor, Zvolensky, McLeish, Bernstein, & Morissette, 2008; Kraemer, McLeish, Jeffries, Avallone, & Luberto, 2013; Zvolensky et al., 2007). These data further indicate that covariation between pain severity and tobacco dependence may serve to impede quitting, possibly due to individual differences in pain-related anxiety.

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Contributors

Authors MZ and KL designed the study and collected the data. Authors JD, JK, EZ conducted the statistical analyses. All authors contributed to the generation of a priori hypotheses, interpretation of the results, and preparation of the manuscript.

Conflict of interest

All authors declare that they have no conflicts of interest.

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