

# **Anxiety and Depression in Bidirectional Relations Between Pain and Smoking: Implications for Smoking Cessation**

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## **Abstract**

Pain and tobacco smoking are highly prevalent and comorbid conditions that impose considerable burdens on individuals and health care systems. A recently proposed reciprocal model suggests that these conditions interact in a bidirectional manner, resulting in greater pain and the maintenance of tobacco addiction. Anxiety and depression are common among smokers in pain and have been identified as central mechanisms of interest. There is emerging evidence that smokers with anxiety/depression may experience more severe pain and functional impairment, greater pain-induced motivation to smoke, and increased sensitivity to pain during periods of smoking abstinence. Based on empirical findings, we hypothesize that these experiences may engender expectations that abstaining from smoking will exacerbate both pain and negative affect, thus eroding self-efficacy for smoking cessation and increasing perceived barriers to quitting. The goal of this narrative review is to examine the role of anxiety/depression in complex pain–smoking relations so as to advance evolving theoretical perspectives and inform the development of tailored interventions.

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The high prevalence and societal impact of both pain and tobacco smoking are substantial and warrant continued research into their etiology and treatment. Moreover, evidence of significant comorbidity between these conditions offers an opportunity to examine mechanisms and modifiable risk factors that can inform the development of novel interventions. One rapidly emerging, yet still understudied area of clinical and empirical interest in complex pain–smoking relations, is the role of co-occurring anxiety and depression (Ditre, Brandon, Zale, & Meagher, 2011). For example, a growing body of evidence suggests that smokers with elevated symptoms of anxiety and depression may experience greater pain and functional impairment, increased motivation to smoke in response to pain, and greater sensitivity to pain when attempting to abstain from smoking. Furthermore, anxiety or depression may amplify the extent to which pain serves as a barrier to smoking cessation. We utilized a narrative approach to review an emerging literature examining the role of anxiety, depression, and related symptoms/sequelae in bidirectional associations between pain and tobacco smoking. It is our hope that this work will inform evolving theoretical perspectives, future research, and the development of tailored smoking treatments for smokers with co-occurring pain and anxious/depressive symptoms.

**Overview of Tobacco Smoking and Pain**

Tobacco smoking is a significant public health problem that is responsible for greater than 40% of all premature deaths and disability in the United States (Centers for Disease Control and Prevention [CDC], 2010), with an estimated annual cost of greater than US\$180 billion in direct medical expenses and lost productivity (CDC, 2008). Despite known health risks, nearly 19% of the U.S. adult population continues to smoke tobacco cigarettes (CDC, 2014). Like smoking, chronic pain is a critical national health concern that affects 22% to 43% of American adults (Gureje et al., 2008; Institute of Medicine [IOM], 2011). Pain is an inherently subjective and aversive experience that is comprised of sensory-physiological, cognitive-evaluative, and motivational-affective components (International Association for the Study of Pain [IASP], 1994; Turk & Melzack, 2011). Chronic pain is typically distinguished from acute pain by applying various pain duration cutoffs (e.g., 3–12 months; Turk & Okifuji, 2001). Pain-related complaints motivate approximately 50% of all physician visits each year, and pain is responsible for greater than US\$600

billion in annual health care costs and lost productivity (IOM, 2011; Mayo Clinic, 2001; Turk & Melzack, 2011).

Complex interrelations between pain and smoking have previously been reviewed and are beyond scope of this article (Ditre et al., 2011; Parkerson, Zvolensky, & Asmundson, 2013; Shi, Weingarten, Mantilla, Hooten, & Warner, 2010). Briefly, prevalence estimates indicate that individuals with chronic pain are about twice as likely to be current smokers relative to individuals without chronic pain (e.g., Strine & Hootman, 2007; Zvolensky, McMillan, Gonzalez, & Asmundson, 2010). Rates of smoking appear to be even higher among clinical pain samples, with several reports indicating that 49% to 68% of treatment-seeking pain patients currently smoke tobacco cigarettes (Hooten, Shi, Gazelka, & Warner, 2011; Jamison, Stetson, & Parris, 1991; Michna et al., 2004). Consistent with the perspective that some individuals may be “burdened” by characteristics that make smoking cessation more difficult (Hughes & Brandon, 2003; Irvin & Brandon, 2000), researchers have suggested that smokers with comorbid pain may constitute a recalcitrant subgroup that faces unique barriers to quitting (e.g., Ditre et al., 2011; Ditre, Langdon, Kosiba, Zale, & Zvolensky, 2015; Zale, Ditre, Dorfman, Heckman, & Brandon, 2014).

According to a recently proposed reciprocal model of pain and smoking (Ditre et al., 2011), interrelations between these conditions may be conceptualized as bidirectional in nature. Based on evidence derived from clinical, epidemiological, and laboratory-based research, this model posits that pain and smoking behavior interact in the manner of a positive feedback loop, resulting in greater pain and the maintenance of tobacco dependence. Research in this emerging domain can be usefully broken down into two directions of empirical inquiry: *the effects of smoking on pain* (e.g., tobacco smoking as a risk factor in the onset of painful conditions) and *the effects of pain on smoking* (e.g., pain as a proximal antecedent of smoking behavior). After examining each of these pathways in turn, we explicate the role of anxiety, depression, and related factors (e.g., negative affect, pain-related anxiety, anhedonia) in complex pain–smoking relations, and discuss implications for smoking cessation and the treatment of tobacco addiction.

## **Bidirectional Relations Between Pain and Tobacco Smoking**

With regard to the *effects of smoking on pain*, there is accumulating evidence that tobacco smoking may worsen pain over time, and that pain may be amplified during the early stages of nicotine withdrawal. Smoking has been identified as a unique causal agent in the development of chronic low back pain

(Shiri, Karppinen, Leino-Arjas, Solovieva, & Viikari-Juntura, 2010) and rheumatoid arthritis (United States Department of Health and Human Services [USDHHS], 2014). Smoking has also been associated with the onset and exacerbation of numerous other painful conditions, including fibromyalgia, chronic headache, and osteoarthritis (Aamodt, Stovner, Hagen, Brathen, & Zwart, 2006; Amin et al., 2007; Goesling et al., 2015; Lee et al., 2010). Relative to nonsmokers, current smokers tend to report greater pain intensity and disability (e.g., pain-related interference with daily activities, work, relationships, physical functioning), and there is some evidence of covariation between pain/disability and severity of tobacco dependence (e.g., Hooten, Shi, et al., 2011; Hooten et al., 2009; Weingarten et al., 2008; Weingarten et al., 2009). Smokers are also more likely to experience deleterious pain treatment outcomes, including greater unemployment (Fishbain et al., 2008), more severe health role limitations (Hooten et al., 2009), and decreased efficacy of pharmacologic/surgical interventions (Glassman et al., 2007; Harty & Veale, 2010; Hooten, Shi, et al., 2011). Finally, smokers may experience greater sensitivity to pain (i.e., hyperalgesia) during periods of smoking abstinence. For example, rodent models have consistently demonstrated increased pain in the context of acute nicotine deprivation (e.g., Grabus, Martin, & Damaj, 2005; Jackson, McIntosh, Brunzell, Sanjakdar, & Damaj, 2009), and initial findings with human participants suggest a positive association between nicotine/tobacco withdrawal and self-reported pain intensity (Allen, Hatsukami, Christianson, & Brown, 2000; Cosgrove et al., 2010).

With regard to the *effects of pain on smoking*, researchers have long recognized that the desire to avoid or mitigate pain may serve as a potent reinforcer in the maintenance of tobacco dependence (e.g., Ditte et al., 2011; Fertig, Pomerleau, & Sanders, 1986; Fishbain et al., 2007; Silverstein, 1982; Zvolensky, McMillan, Gonzalez, & Asmundson, 2009). For example, smokers with chronic pain reliably endorse smoking cigarettes in response to painful episodes (Hooten, Vickers, et al., 2011; Jamison et al., 1991; Patterson et al., 2012). Data derived from ecological momentary assessment and experimental research paradigms further indicate that the experience of pain can increase urge to smoke and function as a proximal antecedent of smoking behavior (Dhingra et al., 2014; Ditte & Brandon, 2008), especially when individuals hold expectations for nicotine/tobacco-related pain reduction (Ditte, Heckman, Butts, & Brandon, 2010). Indeed, new meta-analytic findings show that nicotine delivered via tobacco smoke and other means (e.g., nicotine patch) can produce acute analgesic effects that may be characterized as small to moderate in magnitude (Ditte, Heckman, Zale, Kosiba, & Maisto, under review). Finally, consistent with evidence that pain can motivate smoking, there are some data to suggest that pain may impede smoking cessation.

For example, smokers in pain (relative to no pain) tend to endorse greater difficulty when attempting to quit and less confidence in their ability to remain abstinent during future quit attempts (Ditre, Kosiba, Zale, Zvolensky, & Maisto, under review; Zale et al., 2014). In addition, both acute pain reactivity (Nakajima & al'Absi, 2011) and positive chronic pain status (Waldie, McGee, Reeder, & Poulton, 2008) have been linked with smoking relapse trajectories.

By integrating these directions of empirical inquiry, the reciprocal model of pain and smoking posits that smoking contributes to the onset and exacerbation of pain, which in turn motivates continued smoking, thus resulting in greater pain and the maintenance of tobacco addiction (Ditre et al., 2011). Within this model, negative affect (including the presence of co-occurring anxiety and depression) is hypothesized to play a key mechanistic role, which is consistent with the identification of negative affect as a principal component in theoretical conceptualizations of pain processing (Wade, Dougherty, Hart, Rafii, & Price, 1992) and addiction motivation (Baker, Piper, McCarthy, Majeskie, & Fiore, 2004). Indeed, a growing body of evidence suggests that negative affect mediates pain–smoking relations and exacerbates the deleterious effects of pain on smoking cessation.

## **Anxiety and Depression in Bidirectional Pain–Smoking Relations**

### *Anxiety and Depression*

Anxiety and depression have been related to the onset and maintenance of both chronic pain and tobacco dependence. Whereas anxiety represents the anticipation of future threat, depression represents the presence of sad, empty, or irritable mood (*Diagnostic and Statistical Manual of Mental Disorders [DSM-5]*; American Psychiatric Association [APA], 2013). Symptoms of anxiety and depression can be experienced at varying levels of intensity and duration, with anxious/depressive disorders diagnosed according to established criteria. Thus, individuals may experience symptoms of anxiety or depression without meeting diagnostic criteria for a clinical disorder. Given that either manifestation is likely relevant to complex pain–smoking associations, in the following sections, we refer to *anxiety/depression* when discussing symptoms or disorders, with more granular distinctions made as relevant.

Respective associations between anxiety/depression and both tobacco smoking (e.g., Ameringer & Leventhal, 2010; Morissette, Tull, Gulliver, Kamholz, & Zimering, 2007; Zvolensky et al., 2008) and pain (e.g., Asmundson, Abrams, & Collimore, 2008; Dersh, Polatin, & Gatchel, 2002;

Goesling, Clauw, & Hassett, 2013) have been reviewed extensively. In brief, anxiety/depression tends to be more common and more severe among smokers, relative to nonsmokers (Breslau, 1995; Goodwin et al., 2014; Lasser et al., 2000; McCabe et al., 2004; Williams & Ziedonis, 2004), and has been associated with poorer cessation outcomes (Pratt & Brody, 2010). Similarly, persons with chronic pain (vs. no pain) are more likely to experience anxiety/depression (Currie & Wang, 2004, 2005; de Leeuw, Eisenlohr-Moul, & Bertrand, 2013; Ohayon & Schatzberg, 2003; Torelli, Lambru, & Manzoni, 2006), and those with elevated anxious/depressive symptoms or disorders (i.e., major depressive disorder, panic disorder, and generalized anxiety disorder) tend to experience poorer pain outcomes (e.g., greater pain intensity and disability; Bair, Robinson, Katon, & Kroenke, 2003; Dersh et al., 2002).

Although several studies of pain and smoking have included anxiety symptoms and disorders (i.e., panic disorder, generalized anxiety disorder, social phobia, agoraphobia, specific phobia, posttraumatic stress disorder) as covariates in statistical analyses (Zale & Ditre, 2013; Zvolensky et al., 2009, 2010), few have explicitly tested the mechanistic role of anxiety in pain–smoking interrelations. Research in this area has primarily focused on directional effects of pain on smoking through examination of anxiety states that are more proximal to the pain experience (e.g., pain-related anxiety). According to the fear-avoidance model of chronic pain, pain-related fear and anxiety (i.e., fearful or anxious responding to actual or anticipated pain) are important mechanisms that maintain pain and facilitate the transition from acute to chronic pain (Vlaeyen & Linton, 2000; Zale & Ditre, 2015). There is also emerging evidence that pain-related anxiety may contribute to the maintenance of tobacco dependence. Specifically, among smokers with chronic pain, greater levels of pain-related anxiety have been associated with smoking dependence motives (Ditre, Zale, Kosiba, & Zvolensky, 2013) and expectancies for negative affect reduction via tobacco smoking (Gonzalez, Hogan, McLeish, & Zvolensky, 2010). Smokers who report greater pain-related anxiety have also been shown to endorse greater levels of tobacco dependence and to perceive more barriers to smoking cessation (Ditre et al., 2015). Moreover, researchers have suggested that pain-related anxiety may contribute to the effects of pain on smoking by serving as a situational motivator of smoking, and that smokers who endorse greater levels of pain-related anxiety may favor the use of nicotine/tobacco over other more adaptive strategies for pain coping (Ditre et al., 2015; Ditre et al., 2013).

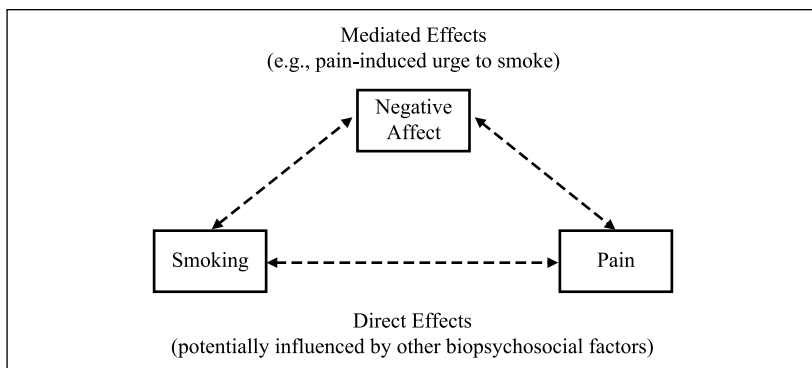
Depression is also highly prevalent among smokers with chronic pain (e.g., Hooten, Shi, et al., 2011; Hooten et al., 2009) and is emerging as a key mediator in directional effects of smoking on pain. For example, Goesling and colleagues (2015) recently found that, among treatment-seeking chronic

pain patients, current smokers endorsed more severe depressive symptoms, which in turn was associated with greater levels of pain and functional interference. Depression was also identified as a mediator of associations between current smoking and both pain severity and pain-related interference among persons evaluated for admission to an outpatient pain treatment program (Goesling, Brummett, & Hassett, 2012). Similar findings derived from a study of patients receiving multidisciplinary pain treatment indicated that greater levels of depressive symptoms partially accounted for associations between current smoking status and pain severity (Hooten, Shi, et al., 2011). Results derived from a population-based study also support the notion that the presence of a major depressive disorder partially accounts for associations between current tobacco smoking and greater pain intensity (van Hecke et al., 2014). Finally, epidemiological data obtained from a nationally representative sample indicate that smoking may contribute to the onset or exacerbation of depressive symptoms, which subsequently may increase the risk of developing chronic pain (Shi, Hooten, Roberts, & Warner, 2010).

In addition to pain onset and severity, we are aware of one study that examined associations among smoking, pain, depression, and opioid analgesic use. Among patients receiving multidisciplinary pain treatment, both depressive symptoms and smoking status were individually associated with greater morphine dosages, but only depressive symptoms were no longer significant when entered simultaneously in a model that included smoking and pain (Hooten, Shi, et al., 2011). These findings suggest that although smoking, pain, depression, and opioid use appear to be interrelated, greater levels of depression among smokers may not be sufficient to account for why they needed higher opioid dosages. It is possible that smoking and opioid use demonstrate unique associations (e.g., above-and-beyond the influence of depression) due to complex nicotine-opioid interactions that can result in cross-tolerance and/or sensitization to the rewarding effects of opioid medications (Shi, Weingarten, et al., 2010; Vihavainen, Piltanen, Tuominen, Korpi, & Ahtee, 2008).

### *Negative Affect and Other Transdiagnostic Factors*

Although assessment of anxiety/depression offers considerable clinical and empirical utility, such broad classifications may obscure shared symptomatology or heterogeneity within disorders. Thus, researchers have also examined factors common across these disorders. First, negative affect represents a broad construct encompassing nonspecific states of subjective distress (Watson, Clark, & Tellegen, 1988), and has been implicated as a mediator in bidirectional pain-smoking relations (see Figure 1). Laboratory research has



**Figure 1.** Negative affect as mediator of bidirectional pain–smoking relations.

consistently demonstrated that negative affect induction (via the presentation of affectively-valenced picture cues) increases both pain sensitivity (e.g., de Wied & Verbaten, 2001; Kenntner-Mabiala, Weyers, & Pauli, 2007; Meagher, Arnau, & Rhudy, 2001; Rhudy, Bartley, & Williams, 2010) and smoking behavior (Kassel, Stroud, & Paronis, 2003), and negative affect is readily elicited through both pain- and smoking-related processes. Indeed, pain-related negative affect is a primary consequence of the pain experience (Wade, Dougherty, Archer, & Price, 1996), and a review of associations between smoking and negative affect concluded that negative affect can be exacerbated by chronic cigarette consumption and smoking withdrawal (Kassel et al., 2003). There is also experimental evidence that pain can be a potent motivator of urge to smoke, with directional effects *partially* mediated by pain-induced negative affect (Ditre & Brandon, 2008). Findings of partial mediation are consistent with the perspective that complex pain–smoking relations are likely driven by a variety of biopsychosocial mechanisms, including, but not limited to, acute negative affective states (Ditre et al., 2011).

In addition to negative affect, transdiagnostic factors (which represent characteristic responses to affective stimuli and states) are of increasing empirical interest. Three such factors were identified in a recent review, which concluded that anhedonia (i.e., diminished pleasure and response to reward), anxiety sensitivity (i.e., fear of anxiety-related sensations), and distress tolerance (i.e., ability to tolerate distressing states) likely serve as common risk factors for both smoking and anxiety/depression, and contribute to the maintenance of tobacco dependence (Leventhal & Zvolensky, 2015). Our review of the literature also indicated that these exemplary factors are highly relevant to chronic pain conditions and may serve as a model for understanding

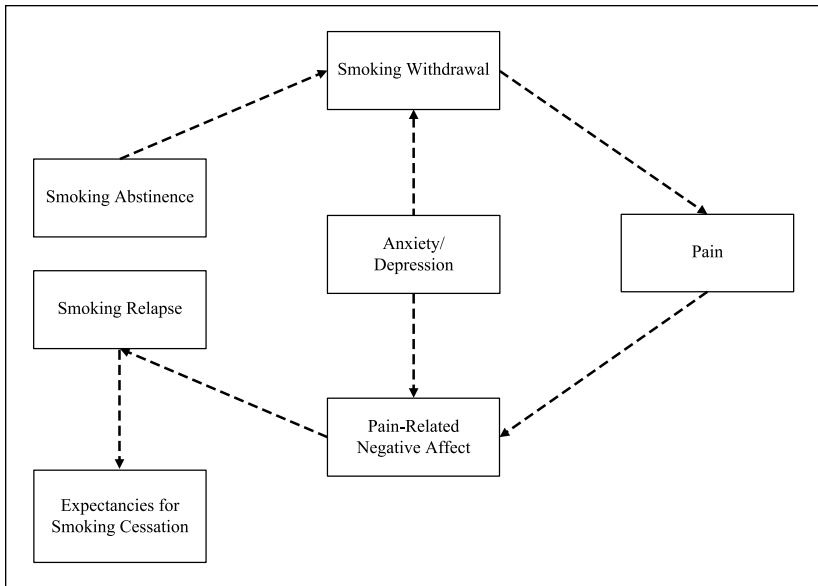


complex associations among pain, smoking, and additional transdiagnostic factors that could be identified in future research. Indeed, chronic pain patients have reported greater levels of anhedonia and decreased responsiveness to rewards, relative to healthy controls (Elvemo, Landrø, Borchgrevink, & Håberg, 2015), and distress tolerance has been implicated in emotion regulation and coping among persons with chronic pain (Hamilton, Karoly, & Kitzman, 2004). Moreover, decades of research have consistently demonstrated that greater levels of anxiety sensitivity predict a range of negative pain-related outcomes, including greater use of analgesic medications, greater cognitive bias toward pain experiences, and greater activation of fear-avoidance mechanisms (e.g., pain-related fear) that contribute to the development and maintenance of pain-related disability (e.g., Asmundson & Norton, 1995; Keogh & Cochrane, 2002; Wong et al., 2014). Thus, we suggest that transdiagnostic factors relevant to anxiety/depression should also be considered when addressing complex interrelations among affect, pain, and tobacco smoking.

## Implications for Smoking Cessation

Within the framework of reciprocal pain–smoking relations, there are several reasons to suspect that anxiety/depression may undermine smoking cessation among persons with chronic pain. As depicted in Figure 2, we hypothesize that anxiety/depression exacerbates tobacco withdrawal severity, which in turn heightens pain sensitivity, resulting in greater negative affect (also potentially amplified by anxiety/depression), and subsequently precipitating relapse to smoking. First, smokers with anxious/depressive symptoms and disorders (e.g., major depressive disorder, panic disorder, generalized anxiety disorder) tend to experience greater levels of nicotine/tobacco withdrawal (i.e., an aversive state characterized by cognitive, affective, behavioral, and physiological symptoms; Hendricks, Ditre, Drobos, & Brandon, 2006; Hughes, 1991) when attempting to abstain from smoking (Leventhal, Ameringer, Osborn, Zvolensky, & Langdon, 2013; Leventhal, Ramsey, Brown, LaChance, & Kahler, 2008; Morissette et al., 2007; Weinberger, Desai, & McKee, 2010). Second, withdrawal severity is a hypothesized mechanism by which smokers may experience greater pain during periods of abstinence (e.g., Allen et al., 2000). Third, researchers have suggested that smokers who experience greater pain and pain-related negative affect during a quit attempt may return to smoking, in part, to alleviate increased pain sensitivity (Ditre et al., 2011; Shi, Weingarten, et al., 2010).

We further hypothesize that repeated experiences of increasingly severe withdrawal and hyperalgesia (i.e., increased sensitivity to pain) when attempting to quit smoking may engender cognitive expectations that



**Figure 2.** Hypothesized role of anxiety and depression in relapse among smokers with chronic pain.

*Note.* Anxiety and depression are hypothesized to exacerbate smoking withdrawal, which increases pain sensitivity, results in greater negative affect, and precipitates relapse to smoking. Repeated cycles are hypothesized to engender negative expectations that undermine future cessation efforts.

abstaining from tobacco will exacerbate both pain and negative affect, thus eroding self-efficacy for smoking cessation and increasing perceived barriers to quitting. Indeed, smokers with chronic pain who endorse greater withdrawal severity during past quit attempts have been shown to anticipate more severe withdrawal/negative affect during future quit attempts (Ditre, Kosiba, et al., under review). Consistent with evidence that past cessation failures may erode confidence for future success (Carey & Carey, 1993; Kirchner, Shiffman, & Wileyto, 2012), smokers in pain have also been shown to report lower levels of self-efficacy and greater perceived barriers to quitting, in part due to having experienced more severe withdrawal and greater difficulty during previous quit attempts (Ditre, Kosiba, et al., under review; Zale et al., 2014). Thus, smokers with comorbid anxiety, depression, and pain may be more likely to encounter difficulty maintaining abstinence, which may engender expectations that ultimately serve to undermine future quit attempts.

## Tailored Approaches to Tobacco Dependence Treatment

Evidence reviewed herein suggests that smokers with comorbid pain and anxiety/depression are likely to experience unique challenges when attempting to quit smoking, and it follows that they may also require specialized treatment. Researchers have suggested that smokers in pain would benefit from tailored interventions that address smoking in the context of pain (e.g., Ditre et al., 2011; Zale et al., 2014), and we further recommend that clinicians also consider the role of anxiety/depression in pain–smoking relations. An integrated cognitive-behavioral approach that encourages consideration of comorbid conditions could provide an optimal model for intervention in this population (Mueser, Noordsy, Drake, & Fox, 2003).

Cognitive-behavioral therapy (CBT) provides the foundation for an efficacious smoking treatment that typically includes psychoeducation, cognitive restructuring, self-monitoring, coping skills training, and self-efficacy enhancement (Brown, 2011; Perkins, Conklin, & Levine, 2008; Reus & Smith, 2008). An integrated CBT-based cessation protocol for smokers with comorbid pain and anxiety/depression could incorporate functional analysis to aid in the identification of pain- and affect/mood-relevant proximal antecedents and consequences of smoking, psychoeducation to prepare these smokers for more severe withdrawal and increased sensitivity to pain during the early stages of a quit attempt, and cognitive restructuring that addresses the perceived utility of smoking for pain coping and affect regulation. Smokers in pain may also benefit from pre-cessation interventions that seek to enhance self-efficacy for quitting by teaching alternative and more adaptive (i.e., non-smoking-related) strategies for coping with both pain and anxiety/depression (e.g., Ditre, Kosiba, et al., under review; Zale et al., 2014).

Recommendations for the treatment of smokers with comorbid psychiatric conditions include the use of combination pharmacotherapy (Fagerstrom & Aubin, 2009), and there is reason to believe that smokers with pain and anxiety/depression may also benefit from tailored combinations of pharmacologic intervention. For example, researchers have suggested that high dose nicotine replacement therapy might confer acute analgesic benefits that help to mitigate pain during the early stages of quitting (Ditre, Heckman, et al., under review). In addition, bupropion is an efficacious smoking cessation aid that is also approved by the Food and Drug Administration (FDA) for treatment of depression (Fiore et al., 2008), and there is some evidence that smokers are less likely to relapse during the early stages of a quit attempt when bupropion and nicotine replacement therapy are combined (Fiore et al., 2008;

Piper et al., 2007). Given evidence that smokers in pain (relative to no pain) are more likely to utilize pharmacotherapy for smoking cessation (Zale & Ditre, 2013), they may be especially amenable to dual treatment (e.g., bupropion plus combination/high dose nicotine replacement therapy).

## Conclusion and Future Research Directions

Our review of the literature indicates that chronic pain and anxiety/depression each make smoking cessation more difficult, and that their co-occurrence may impede quitting to a greater extent than either in isolation. Specifically, we observed evidence that pain, smoking, and anxiety/depression are all highly prevalent and comorbid, and that negative affect is a likely mediator of reciprocal pain–smoking relations. We also integrated parallel lines of research to suggest that anxiety/depression may exacerbate the deleterious effects of pain on smoking cessation via processes such as greater pain-induced motivation to smoke, more severe withdrawal, and increased sensitivity to pain. Limitations of the currently reviewed literature include variability in the assessment of anxiety/depression, recent adjustments to the criteria used to classify and diagnose anxious/depressive disorders (*DSM-5*, APA, 2013), and relatively few studies that directly tested interrelations among pain, smoking and anxiety/depression. Additional research is needed to better understand the complex interplay of pain and anxiety/depression during the course of a smoking cessation attempt, and several promising lines of research warrant discussion.

First, ecological momentary assessment methods have recently been used to track near real-time covariation of pain intensity and smoking behavior (Dhingra et al., 2014), and future studies should apply these techniques to monitor temporal changes in pain intensity, anxiety/depression, negative affect, and withdrawal severity during the early stages of smoking abstinence. Future research would also benefit from assessing covariation between smoking-related outcome expectancies (Pain and Smoking Inventory; Ditre, Zale, Heckman, & Hendricks, under review) and transdiagnostic factors (Leventhal & Zvolensky, 2015) that are relevant to anxiety, depression, negative affect pain, and smoking prior to and over the course of a smoking cessation attempt. Although our review identified exemplary transdiagnostic factors that have been studied extensively for their role in associations between smoking and anxiety/depression, future work should seek to identify additional factors (e.g., pain catastrophizing) that may play an important role in bidirectional pain–smoking relations.

Future research would also benefit from examining overlap in neurobiological substrates associated with anxiety/depression, smoking behavior, and

pain perception (Parkerson et al., 2013). For example, corticotropin-releasing factor (CRF) has been identified as a potential mechanism in the effects of pain on smoking (Ditre et al., 2011), and rodent models of nicotine self-administration implicate CRF1 receptors in the manifestation of anxiety-like behavior and increased pain during nicotine deprivation (Cohen et al., 2015). There is also an emerging consensus that activation of nicotinic acetylcholine receptors (nAChRs) plays a prominent role in pain–smoking processes. Greater nAChR availability has been associated with increased pain reactivity during smoking abstinence among humans (Cosgrove et al., 2010), and recent animal studies indicate that nAChR subunits that modulate nicotine analgesia are central in expression of anxiety- and depression-like behaviors (Semenova, Contet, Roberts, & Markou, 2012). Additional work is needed to better understand how overlapping neural mechanisms may contribute to the maintenance of tobacco dependence among smokers with comorbid chronic pain and anxiety/depression, as this work may also inform novel pharmacologic intervention approaches.

Finally, it is necessary to conduct randomized-controlled trials to test the utility of existing and novel smoking cessation treatments for smokers with comorbid pain and anxiety/depression. For example, it is not yet known whether treatment of anxiety/depression prior to a quit attempt (i.e., sequential treatment) may either aid in the management/mitigation of pain during smoking abstinence or decrease the extent to which pain precipitates relapse. Future research is also needed to better understand potentially complex interrelations between pain, smoking, anxiety/depression and opioid use. For example, researchers should examine whether concurrent opioid use influences the treatment of tobacco dependence and anxiety/depression among smokers in pain. Pilot data suggest that varenicline (a prescription medication for smoking cessation) may be efficacious for the treatment of opioid tapering (Hooten & Warner, 2015), and additional research is needed to determine whether smokers who seek to taper their opioid medications should do so in conjunction with a quit attempt. Although we have suggested that some evidence-based treatments could be adapted to benefit smokers with chronic pain and anxiety/depression, such interventions have yet to be developed or tested. Future research may consider the utility of sequential and/or integrated treatments for pain and smoking cessation among individuals with comorbid anxiety and depression.

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