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ORIGINAL ARTICLE

The Role of Anxiety-Relevant Transdiagnostic Factors in Comorbid Chronic Pain and Tobacco Cigarette Smoking

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Abstract

Despite the notable prevalence and comorbidity of tobacco cigarette dependence and chronic pain, relatively little is known about potential mechanisms of action. Research has emphasized the utility of identifying core underlying dimensions that reflect shared etiological processes, and it has been posited that anxiety-relevant transdiagnostic factors may be particularly important to understanding pain-smoking comorbidity. This review examined the empirical literature linking pain-related fear (fear of pain and activities that elicit pain), pain-related anxiety (anxious responses to pain), and anxiety sensitivity (degree to which the experience of anxiety is expected to have deleterious consequences) to both chronic pain and tobacco cigarette smoking. We then integrated this literature to inform a conceptual model explicating the function of anxiety-relevant transdiagnostic factors in pain-tobacco smoking comorbidity. Finally, we drew upon this conceptual model to highlight novel clinical implications and inform future research.

Keywords Pain · Anxiety · Tobacco · Smoking · Transdiagnostic

Tobacco cigarette smoking and pain are each significant public health problems that produce a combined economic impact (primarily via medical costs and reduced productivity) of more than $840 billion each year (IOM 2011, US Department of Health and Human Services 2014). Among individuals living in the United States, chronic pain (often defined as pain lasting longer than standard healing time or greater than 3 months; Turk and Okifuji 2001) affects more than 100 million adults (IOM 2011). In addition, approximately 15% of all U.S. adults continue to smoke tobacco cigarettes (Jamal 2016). Rates of tobacco smoking among individuals with co-occurring pain are higher than in the general population (24–68%; e.g., Michna et al. 2004; Orhurhu et al. 2015; Zvolensky et al. 2009).

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Associations between pain and tobacco use are bidirectional, leading to deleterious pain outcomes and continued smoking (Ditre et al. 2011; Zale et al. 2016). Accordingly, tobacco use has been connected to the onset and worsening of chronic pain (e.g., Boogaard et al. 2015; Shiri et al. 2010; Sugiyama et al. 2010), regular smokers often report more pain and disability than nonsmokers (e.g., Hooten et al. 2011), and smoking urges and behaviors can be motivated by painful experiences (Dhingra et al. 2014; Ditre and Brandon 2008; Ditre et al. 2010; Parkerson and Asmundson 2016). Smokers with co-occurring pain report greater difficulty quitting than smokers without pain (Ditre et al. 2016; Zale et al. 2014), and experimental evidence suggests that daily smokers may become more sensitive to painful stimuli (Ditre et al. 2018). Given that nicotine can reduce pain (e.g., Ditre et al. 2016), it is possible that smokers who are attempting to quit may relapse as a function of abstinence-induced exacerbation of pain.

To gain a better understanding of etiologic mechanisms underlying pain-smoking comorbidity, and to advance clinical practice for smokers with comorbid chronic pain, there should be an increased emphasis on the identification of transdiagnostic processes that have been implicated in both chronic pain and nicotine dependence. A recent review found that both pain and anxiety can impede smoking cessation and noted that

their co-occurrence may make quitting even harder (Zale et al. 2016). Zale et al. further suggested that future work should aim to identify anxiety-relevant transdiagnostic factors that underlie pain-smoking comorbidity.

We are not aware of any previous reviews that examined anxiety-relevant transdiagnostic factors in the co-occurrence of tobacco smoking and pain. The goals of this narrative review were to (1) review the literature linking two anxiety-relevant transdiagnostic factors (i.e., pain-related fear and anxiety sensitivity) to pain and smoking; (2) propose a transdiagnostic model that highlights the potential role of these factors in pain-smoking comorbidity; and (3) draw upon this conceptualization to underscore clinical implications and provide guidance for future research initiatives. The current review focuses on pain-related fear (fear of pain and activities that elicit pain), the related construct of pain-related anxiety (anxious responses to pain), and anxiety sensitivity (degree to which the experience of anxiety is expected to have deleterious consequences), largely because previous work has documented the theoretical and empirical applicability of these factors to both chronic pain and tobacco dependence (e.g., Asmundson 1999; LaRowe et al. 2017; Leventhal and Zvolensky 2015; Zale and Ditre 2015). Although pain-related fear and anxiety sensitivity have been positively associated with one another (e.g., Asmundson and Norton 1995; Carleton and Asmundson 2009; Gonzalez et al. 2011), they are believed to reflect distinct processes with each demonstrating unique validity in predicting pain and associated outcomes (e.g., Carleton et al. 2009; Keogh et al. 2010).

Relevant articles were identified via computer database searches of *PubMed* and *PsycINFO*. Specifically, searches in PubMed utilized the search terms: ("pain-related fear" OR "pain-related anxiety" OR "anxiety sensitivity") AND ("chronic pain" OR "smoking" OR "cigarette" OR "nicotine"), and searches in PsycINFO utilized the same search terms with all terms limited to keyword searches. Returned references were combined and duplicates were removed, resulting in a total of 495 articles. Titles and abstracts were screened, and papers were excluded if they were not published in a peer-reviewed journal (k = 10), recruited samples of children/pediatric patients (k = 41), used non-human samples (k = 4), or did not examine associations between pain-related fear, pain-related anxiety, or anxiety sensitivity and either chronic pain or tobacco smoking-relevant outcomes (k = 218). Thus, a total of 222 full-text articles were examined and considered for inclusion in the current narrative review.

Pain-Related Fear

Pain-related fear encompasses fear of painful sensations and activities that may theoretically worsen pain (e.g., Zale and Ditre 2015). Neural correlates of pain-related fear have been identified, including the activation of brain regions associated with response regulation (e.g., Ochsner et al. 2006). The Fear Avoidance Beliefs Questionnaire is a commonly used measure of pain-related fear that assesses beliefs about how physical activity and work-related activities may exacerbate the pain experience (Waddell et al. 1993).

Pain-related anxiety reflects the propensity to experience anxiety in response to pain (McCracken and Dhingra 2002; McCracken et al. 1992). Two common indices of pain-related anxiety include the original Pain Anxiety Symptom Scale (McCracken et al. 1992) and a revised 20-item version (McCracken and Dhingra 2002). Both measures ask respondents to indicate the frequency in which they engage a variety of pain-related thoughts and behaviors. Both measures assess four subcomponents of pain-related anxiety, including physiological anxiety (e.g., "Pain seems to cause my heart to pound or race"), escape or avoidance (e.g., "I avoid important activities when I hurt"), fearful appraisals (e.g., "When I feel pain, I am afraid that something terrible will happen"), and cognitions (e.g., "I can't think straight when in pain"; McCracken and Dhingra 2002).

Pain-related fear and pain-related anxiety are related, yet distinct constructs. Although additional work is needed to fully disentangle the relationship between pain-related fear and pain-related anxiety, theoretical conceptualizations suggest that fear involves a visceral, mobilization for action ("fight-flight-freeze") in response to a threat, whereas anxiety involves a cognitive-affective response in the absence of a readily identifiable threat (Zinbarg et al. 1997). Consistent with these perspectives, fear typically motivates defensive behaviors (e.g., escape), whereas anxiety typically motivates preventative behaviors (e.g., avoidance; Leeuw et al. 2007). It has further been noted that distinctions between pain-related fear and anxiety may be less evident in clinical contexts, particularly among chronic pain patients who tend to experience the threat (i.e., pain) with greater frequency (e.g., Leeuw et al. 2007). Despite this, previous studies have independently measured and investigated pain-related fear and pain-related anxiety (e.g., Zvolensky et al. 2001).

Pain Related Fear and Chronic/Recurring Pain

A fear-avoidance model of chronic pain posits pain-related fear as a maintaining factor in the experience of pain that can facilitate the transition from acute to chronic pain (e.g., Crombez et al. 1999; Vlaeyen and Linton 2000). This model suggests that pain-related fear provokes escape and avoidance behaviors in response to actual or anticipated pain, leading to increased functional disability and impairment (e.g., Crombez et al. 1999). Avoidance occurs in anticipation of pain, whereas escape behaviors occur in response to pain. Avoidance tends to persist because there are fewer learning opportunities to correct expectancies regarding pain as a

signal of threat to functional well-being. Over time, avoidance and physical inactivity can have deleterious effects on various physiological systems (e.g., musculoskeletal and cardiovascular), resulting in greater pain and disability (Crombez et al. 1999).

A previous review described empirical evidence supporting the notion that pain-related fear contributes to the onset of acute pain, transition to chronic pain, and the worsening of pain intensity/interference (Turk and Wilson 2010). Turk and Wilson (2010) determined that pain-related fear is an important factor to address when developing and implementing interventions for chronic pain patients. Indeed, among individuals with recurring pain, pain-related fear has been positively associated with ratings of perceived pain intensity (Boersma and Linton 2006), pain-related disability (Boersma and Linton 2006; Vlaeyen et al. 1995), and expectations that pain will become a persistent problem (Boersma and Linton 2006). Higher levels of pain-related anxiety have similarly been associated with greater pain (McCracken et al. 1993) and more frequent reports of reporting physical complaints (McCracken et al. 1998). In addition, some evidence suggests that there may be a negative association between pain-related anxiety and indices of pain tolerance. For example, one relatively small laboratory study found that scores on each of the Pain Anxiety Symptom Scale subscales (i.e., escape and avoidance, fear, cognitive anxiety, and physiological anxiety) were negatively correlated ($rs = .456–.628$) with tolerance to cold pressor pain induction among 27 female participants who experience chronic tension headaches (Bishop et al. 2001).

Importantly, measures of pain-related anxiety appear to be stronger predictors of pain intensity, disability scores, and pain-related behaviors, than non-pain specific measures of anxiety and fear among treatment-seeking chronic pain patients (McCracken et al. 1996). Some evidence further suggests that subcomponents of pain-related anxiety may predict different outcomes. For example, the escape and avoidance dimension has evinced utility as a strong predictor of pain interference, avoidance behavior, and disability (McCracken et al. 1996; Vowles et al. 2004). Collectively, these findings underscore the importance of considering unique facets of pain-related anxiety when examining relations with other symptoms and disorders.

Several studies have also examined mechanisms that may underlie observed positive associations between pain-related fear/anxiety and indices of pain severity and physical disability. Greater pain-related fear has been related to attentional interference and selective bias towards attending to pain-related information among both chronic pain and undergraduate samples (Crombez et al. 1999; Keogh et al. 2001). In addition, higher pain-related anxiety has been correlated with a tendency to over-predict pain (McCracken et al. 1993) and employ maladaptive pain-coping responses (e.g., catastrophizing) among male and female patients referred to a pain management clinic (McCracken and Gross 1993). Interestingly, a study consisting of chronic pain patients found that relations between pain outcomes (e.g., pain severity, disability) and pain-related anxiety were only evident among males (Edwards et al. 2000). Collectively, this corpus of work suggests that positive associations between pain-related fear and chronic pain may be explained, in part, by biases in attending to pain, as well as the use of maladaptive coping techniques, perhaps moderated by biological sex.

Treatments targeting pain-related fear and pain-related anxiety among individuals with chronically painful conditions have previously been reviewed (Bailey et al. 2010). Bailey et al. (2010) concluded that graded in vivo exposure, and acceptance and commitment therapy, each appear to contribute to greater decreases in disability and fear of pain among individuals with chronic musculoskeletal pain, when compared to graded activity interventions or a wait-list-control conditions (Bailey et al. 2010). It is also worth noting that prospective research has revealed associations between positive pain treatment outcomes and reductions in self-reported pain-related anxiety. Indeed, greater pre- to post-treatment decreases in pain-related anxiety have consistently predicted reduced pain intensity (McCracken et al. 2002; McCracken and Gross 1998) and less pain-related disability/interference (McCracken et al. 2002; McCracken and Gross 1998). Importantly, scores on measures of pain-related anxiety continue to predict these outcomes after accounting for other typically comorbid factors, including depression (McCracken and Gross 1998) and physical capacity (McCracken et al. 2002).

Pain-Related Fear and Tobacco Cigarette Smoking

Negative reinforcement models of addiction consider negative reinforcement to play an important role in the motivation of substance use (Ahmed and Koob 2005; Baker et al. 2004), and it has been proposed that smokers who report elevated pain-related fear may also be more likely to use tobacco for pain coping purposes (LaRowe et al. 2017). Self-medication models of addiction further specify a pharmacological link between the use of a given substance and underlying distress (Khantzian 1997), and smokers with high pain-related fear may attempt to self-medicate their pain with nicotine (Ditre et al. 2016). In addition, given that smoking abstinence may lead to increased pain reporting (LaRowe et al. in press) and greater sensitivity to pain (Ditre et al. 2018), smokers who endorse elevated levels of pain-related fear may be at greater risk for relapsing during the initial phases of smoking cessation.

In chronic pain populations, current smokers tend to report greater pain-related anxiety than non-smokers (Hooten et al. 2009). Smokers with higher (vs. lower)

pain-related anxiety may be more prone to endorse cigarette smoking as a strategy for coping with pain (Patterson et al. 2012). Moreover, scores on measures of pain-related anxiety have been positively correlated with core topographies of tobacco dependence and situational motivators of smoking (Ditre et al. 2015). Specifically, pain-related anxiety was found to account for 20% of unique variability in smoking dependence scores among persons with chronic pain, even after statistically controlling for a variety of pain, anxiety, and sociodemographic factors (Ditre et al. 2013).

Studies conducted among community samples of daily tobacco cigarette smokers have found pain-related anxiety to be related with self-reported smoking cessation barriers, and robust expectations that nicotine/tobacco can reduce negative affect (Ditre et al. 2015; Gonzalez et al. 2010). One prospective study showed that high pain-related anxiety scores predicted a greater likelihood of both lapse and relapse to smoking in the context of a self-guided cessation attempt (LaRowe et al. 2017). More specifically, every one-point increase on a 100-point measure of pain-related anxiety predicted an approximately 4% increased risk for early lapse/relapse to smoking. Taken together, these findings demonstrate that pain-related anxiety may play an important role in the maintenance of tobacco dependence.

Anxiety Sensitivity

Anxiety sensitivity reflects the extent to which anxiety and anxiety-relevant experiences are expected to provoke deleterious consequences (Reiss 1985). Individuals with high anxiety sensitivity tend to fear interoceptive sensations suggestive of arousal/anxiety, at least in part because they believe these experiences may produce negative outcomes (e.g., heart attack). Anxiety sensitivity has been positively correlated with the activation of prefrontal brain regions that influence self-focused attentional processes (Ochsner et al. 2006). The anxiety sensitivity construct is believed to consist of physical, mental, and social fear components (Zinbarg et al. 1997), and is often assessed using the Anxiety Sensitivity Index (Reiss et al. 1986), the Anxiety Sensitivity Index-3 (Taylor et al. 2007), and the Anxiety Sensitivity Index-Revised (Taylor and Cox 1998). These measures ask respondents to indicate their agreement with several statements that cover physical, mental, and publicly observable experiences.

Anxiety Sensitivity and Chronic/Recurring Pain

Anxiety sensitivity plays a role in amplifying various fears (e.g., Reiss 1991), and it has been posited that this cognitive factor may influence the degree to which individuals fear and attempt to escape/avoid pain (Asmundson 1999). Accordingly, recent conceptualizations of the fear-avoidance model have noted the influence of anxiety sensitivity in the maintenance of pain over time, and in the exacerbation of pain-related suffering (Asmundson 1999).

Empirical associations between chronic pain and anxiety sensitivity have previously been reviewed (Asmundson 1999; Stewart and Asmundson 2006), and a more recent meta-analytic study indicated that anxiety sensitivity was positively associated with the severity of painful experiences (Ocañez et al. 2010). Among clinical pain samples, this meta-analysis revealed: (1) a large effect in the association between fear of pain and anxiety sensitivity, (2) a medium to large effect in the association between pain-related negative affect and anxiety sensitivity, and (3) small to medium effects in associations between pain severity/disability and anxiety sensitivity (Ocañez et al. 2010). Collectively, these findings suggest that greater endorsement of anxiety sensitivity is linked to amplification of pain-related somatic experiences, maladaptive avoidance behaviors, and physical disuse (Ocañez et al. 2010). Given that anxiety sensitivity-pain relations have previously been reviewed, we limit the following section to a summary of data implicating anxiety sensitivity as a maintaining factor in the course of chronically painful conditions.

Chronic pain patients with elevated levels of anxiety sensitivity tend to report greater cognitive interference, increased anxiety in reaction to painful experiences, and greater use of pain-relieving medications (Asmundson and Norton 1995; Asmundson et al. 1999). Patients with elevated levels of anxiety sensitivity are more prone to try and escape or avoid pain (Asmundson et al. 1999), which may be explained by pain-related fear (Norton and Asmundson 2004). Although two early studies failed to observe an association pain tolerance and scores on a measure of anxiety sensitivity (Keogh and Birkby 1999; Keogh et al. 2001), a more recent study did observe an inverse association between anxiety sensitivity and tolerance to experimental pain induction (Esteve and Camacho 2008). Notably, Keogh et al. (2001) and Esteve and Camacho (2008) each limited recruitment to female participants, and some research indicates that elevated anxiety sensitivity may be associated with endorsement of greater sensory and affective pain experiences during experimental pain induction among female, but not male, participants (Keogh and Birkby 1999; Keogh and Cochrane 2002; Keogh et al. 2001). A cross-sectional study of chest pain patients also revealed that positive associations between anxiety sensitivity and pain were only evident among women (Keogh et al. 2004).

Prospective data further indicate that greater anxiety sensitivity may lead to more severe pain-related consequences. For example, higher anxiety sensitivity during mid-pregnancy has been shown to predict maximum and sensory labor pain among mothers (Lang et al. 2006). Similarly,

anxiety sensitivity assessed prior to dental excavation and filling was found to be positively related to both intensity and affective components of the post-procedural pain experience (Klages et al. 2006). Finally, among patients recruited from a hospital bone fracture clinic, anxiety sensitivity was linked to more severe disability, after accounting for other injury-related factors (Keogh et al. 2010).

Given robust empirical evidence of a positive relation between chronic pain severity and self-reports of anxiety sensitivity, some studies have begun to consider the utility of addressing anxiety-relevant amplification of affective and sensory pain experiences (Flink et al. 2009; Watt et al. 2006). Initial work suggests that such treatments offer promise in terms of increasing pain acceptance and reducing pain-related anxiety and distress (Flink et al. 2009; Watt et al. 2006). For example, an intervention that employed interceptive exposure to pain sensations resulted in moderately high improvements in acceptance of pain, as well as decreased levels of pain-related distress (Flink et al. 2009).

Anxiety Sensitivity and Tobacco Cigarette Smoking

Cigarette smoking can reduce anxiety (Kassel and Unrod 2000), and smokers with high anxiety sensitivity may use tobacco to cope with anxiety. Moreover, such smokers may be at greater risk for relapse following a cessation attempt, in part, to alleviate abstinence-induced increases in anxiety (Hughes and Hatsukami 1986). Empirical relations between anxiety sensitivity and smoking have previously been reviewed, and anxiety sensitivity has been posited as a transdiagnostic factor in the progression of tobacco addiction (Leventhal and Zvolensky 2015). Consistent with this perspective, greater levels of self-reported anxiety sensitivity have been linked to a greater likelihood of current smoking (vs. current nonsmoking) among individuals with comorbid anxiety disorders (McCabe et al. 2004; Morissette et al. 2006), and those recruited from the local community (Avallone and McLeish 2015). Even prior to smoking initiation, individuals with high anxiety sensitivity may develop expectancies that smoking can reduce anxiety, due to observations of other smokers and experience with other substances (Leventhal and Zvolensky 2015; O'connor et al. 2008).

Daily smokers with high (vs. low) anxiety sensitivity tend to smoke more cigarettes per day (Bakhshaie et al. 2016), and score higher on measures of tobacco dependence (e.g., Bakhshaie et al. 2016). Such associations may be due, in part, to the indirect effects of smoking-specific avoidance and inflexibility (Bakhshaie et al. 2016). It has also been found that perceived health may function as a moderator of positive relations between smoking rate and anxiety sensitivity (McLeish et al. 2006).

A variety of tobacco smoking motives have also been positively associated with anxiety sensitivity, including smoking for addictive (e.g., to satisfy a craving) and habitual/automatic (e.g., smoking without remembering putting a cigarette in one's mouth) reasons (Leyro et al. 2008; Tiffany and Carter 1998), and the self-administration of tobacco for positive or negative reinforcement (e.g., Battista et al. 2008). Individuals who smoke tobacco and score high on measures of anxiety sensitivity have also been shown to endorse a greater number of perceived barriers to quitting smoking (Gonzalez et al. 2008; Zvolensky et al. 2014), and they tend to hold stronger beliefs that cigarette smoking can ameliorate negative affect (e.g., Johnson et al. 2008, 2013; Zvolensky et al. 2004).

In addition, cross-sectional studies that asked daily male and female smokers to report the longest period they were able to abstain from smoking observed medium to large effects of anxiety sensitivity on the likelihood of reporting an early relapse to smoking (Zvolensky et al. 2006). Prospective research corroborates the notion that anxiety sensitivity can predict risk of smoking lapse and relapse (Brown et al. 2001; Mullane et al. 2008; Zvolensky et al. 2009). Moreover, among daily smokers participating in an "anxiety sensitivity reduction-smoking cessation" intervention trial, those with elevated anxiety sensitivity at baseline evinced the lowest degree of pre-quit reduction in anxiety sensitivity and went on to experience the highest levels of quit-day cigarette craving (Bakhshaie et al. 2016). Finally, there is evidence of covariation between anxiety sensitivity scores and nicotine withdrawal symptoms over the course of a smoking cessation attempt among daily smokers who are motivated to quit (e.g., Bakhshaie et al. 2018), and there is reason to suspect that anxiety sensitivity may play an even more important role in the context of elevated negative affect (Langdon et al. 2015).

Treatments that employ psychoeducation, interoceptive exposure, and cognitive restructuring to decrease anxiety sensitivity have been incorporated into smoking cessation interventions. For example, one 16-session anxiety sensitivity plus smoking cessation intervention resulted in decreased anxiety sensitivity from pre- to post-treatment, and improved cessation outcomes (Zvolensky et al. 2003). Randomized controlled trials have continued to demonstrate the utility of incorporating treatments aimed at reducing anxiety sensitivity into standard smoking cessation interventions. For example, a single session program was shown to reduce both smoking rate and self-reported anxiety for up to 1-month post-treatment among daily adult smokers (Feldner et al. 2008). Another eight-session smoking cessation treatment for individuals who endorsed high levels of pre-quit anxiety sensitivity found that anxiety sensitivity was reduced and cessation success was maintained up to 3 months post-quit (Zvolensky et al. 2008, 2014). This program incorporated cognitive restructuring, exposure to anxiety-related sensations, and acceptance-based behavioral counseling.

Similarly, a smoking cessation intervention that incorporated vigorous exercise led to higher 7-day point prevalence abstinence rates among individuals who scored high, relative to low, on a baseline assessment of anxiety sensitivity (Smits et al. 2016). This smoking cessation plus exercise intervention was also shown to be more successful at reducing anxiety sensitivity and rates of smoking abstinence up to 6-months post-quit, relative to smoking cessation plus wellness education (Zvolensky et al. 2018). Indeed, aerobic exercise elicits sensations that can provoke anxiety reactions (e.g., increased heart rate, perspiration), and repeated exposures to these sensations via exercise may extinguish fear responses and decrease anxiety sensitivity (Broman-Fulks et al. 2004). Most recently, a relatively large ($N = 529$) randomized controlled trial found that an integrated anxiety reduction plus smoking cessation intervention was more effective in reducing anxiety sensitivity among treatment-seeking daily smokers, compared to a standard cessation treatment (Zvolensky et al. 2018). There was also an indirect treatment effect on point prevalence abstinence via anxiety sensitivity reduction.

An Integrative Model Linking Anxiety-Relevant Transdiagnostic Vulnerabilities to Comorbid Chronic Pain and Tobacco Cigarette Smoking

We propose that pain-related fear and anxiety sensitivity function as transdiagnostic factors underlying pain-smoking comorbidity (see Fig. 1).

The current literature review suggests that pain-related fear and anxiety sensitivity can directly amplify the propensity to escape and avoid actual or anticipated pain and anxiety. In accordance with fear-avoidance perspectives of chronic pain (Vlaeyen and Linton 2000), pain-related escape and avoidance behaviors lead to disuse (i.e., prolonged physical inactivity), which in turn contributes to the progression of chronic pain, more severe pain intensity, and greater functional impairment. Informed by negative reinforcement perspectives of addiction motivation (Baker et al. 2004), we further hypothesize that pain-related fear and anxiety sensitivity can increase the actual and anticipated analgesic and anxiolytic effects of smoking. Thus, individuals who experience more pain-related fear and anxiety may come to derive greater negative reinforcement from smoking, contributing to ongoing tobacco dependence. Given that pain and tobacco use trajectories are considered to be bidirectional in nature (Ditre et al. 2011), it is also plausible that pain-related fear and anxiety sensitivity may amplify pain-smoking reciprocity.

Pain-related fear (including pain-related anxiety) and anxiety sensitivity have been implicated in both chronic pain and tobacco cigarette dependence, and we conceptualize them as transdiagnostic vulnerability factors that may represent valuable targets for intervention. Indeed, transdiagnostic treatment protocols apply identical underlying treatment principles without tailoring for specific symptoms or disorders (McEvoy et al. 2009). Compared to diagnosis-specific protocols, transdiagnostic interventions can be more efficient at treating comorbid conditions (vs. sequentially treating each disorder) by facilitating the generalization of treatment effects across disorders in a more time and cost-effective manner (e.g., McEvoy et al. 2009).

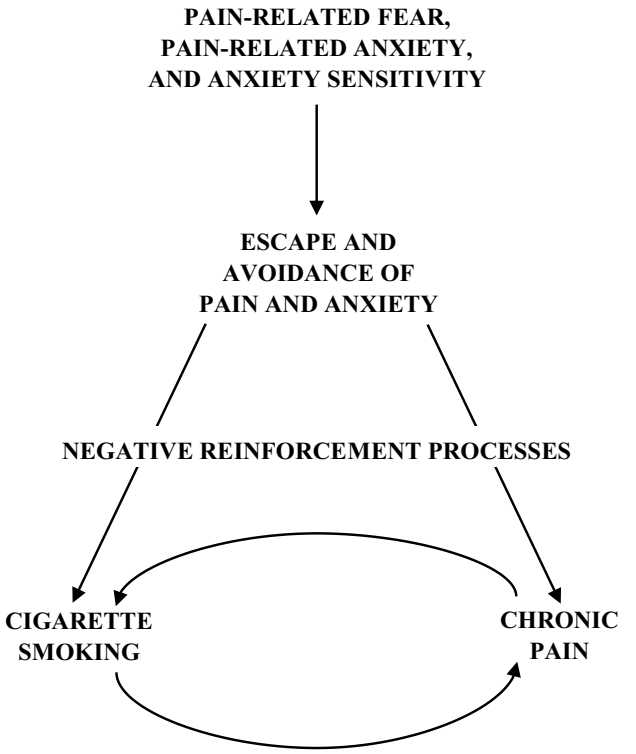

Fig. 1 Integrative model linking pain-related fear and anxiety sensitivity to comorbid chronic pain and cigarette smoking

Transdiagnostic interventions that target pain-related fear and anxiety sensitivity may simultaneously decrease pain and tobacco dependence. A transdiagnostic treatment protocol for comorbid chronic pain and tobacco smoking may include functional analysis to elucidate antecedents and consequences of escape and avoidance behaviors (e.g., smoking, disuse; Haynes and O'Brien 1990). In addition, such protocols may aim to decrease pain-related fear and anxiety sensitivity via graded exposure to both pain (e.g., bending over to pick up an object, jumping up and down; Bailey et al. 2010) and anxiety-provoking interoceptive cues (e.g., spinning, narrow straw breathing; Boswell et al. 2013). Interventions that challenge biases and maladaptive automatic cognitive appraisals of pain (e.g., "Physical activity might harm my back") and anxiety (e.g., "When I notice that my heart

is beating rapidly, I worry that I might have a heart attack") may also contribute to the reduction of both pain-related fear and anxiety sensitivity (e.g., Leahy 1996). Finally, cognitive restructuring could address outcome expectancies that smoking can confer benefits regarding pain-coping and anxiety regulation (e.g., Ditre et al. 2017).

Transdiagnostic treatments for smokers with chronic pain may also incorporate psychoeducation to prepare individuals for smoking abstinence-induced exacerbation of nicotine withdrawal (Ditre et al. 2016), anxiety (Hughes and Hatsukami 1986), and pain (Ditre et al. in press). Prior to a quit attempt, it can be beneficial to offer smokers treatments that are designed to increase self-efficacy for quitting. Such interventions may involve teaching smokers with co-occurring pain to utilize more adaptive strategies for pain- and anxiety coping. Pharmacotherapy for smoking cessation is another potentially important transdiagnostic consideration, as nicotine replacement therapy could aid in mitigating both pain and nicotine withdrawal throughout the initial phases of cessation (Ditre et al. 2016).

A transdiagnostic approach to treating comorbid chronic pain and tobacco cigarette dependence may confer numerous benefits relative to traditional, more isolated treatment approaches. However, several important gaps in the empirical literature remain. For example, although there is compelling evidence that pain-related fear and sensitivity to anxiety contribute to both pain and tobacco smoking trajectories, the processes by which pain-related fear and anxiety sensitivity may influence the co-occurrence of these conditions remains poorly understood. Future work should examine whether individuals with comorbid chronic pain and tobacco dependence tend to experience greater pain-related fear and anxiety, in comparison to smokers without chronic pain and non-smokers who live with recurring pain. Future work should also test how these factors influence pain-induced smoking urge and consumption behavior (Ditre and Brandon 2008), pain-smoking expectancies (Ditre et al. 2017), and the experience of smoking abstinence-induced hyperalgesia (Ditre et al. in press). In addition, although fear of pain encompasses both the fear of painful sensations and activities that may worsen pain, the Fear Avoidance Beliefs Questionnaire only focuses on fearful appraisals of pain in the context of physical activity and work-related activities. Thus, future work is needed to examine associations between fear of pain in the absence of activities that may exacerbate discomfort (e.g., fear of pain sensations) and both chronic pain and smoking-related outcomes.

Future work should also examine the mechanisms by which greater pain-related fear and anxiety sensitivity may exacerbate comorbid chronic pain and tobacco smoking among some individuals, but not others (i.e., divergent trajectories). Along these lines, it remains unclear how pain-related fear and anxiety sensitivity contribute to the etiology of divergent pain trajectories (e.g., neuropathic vs. musculoskeletal; widespread vs. specific area). Future work should also identify moderating factors that determine whether high pain-related fear and anxiety sensitivity lead to some disorders or and not others (Nolen-Hoeksema and Watkins 2011). For example, future research should test the extent to which biological sex moderates the effects of pain-related fear and anxiety sensitivity on comorbid pain and tobacco smoking (Edwards et al. 2000; Keogh et al. 2004).

Although this review was centered on the constructs of pain-related fear and anxiety sensitivity in pain-smoking comorbidity, other potential transdiagnostic factors likely warrant empirical consideration as well. For example, emerging evidence indicates that distress intolerance may play a transdiagnostic function in comorbid pain and tobacco dependence. Indeed, distress intolerance has been associated with continued tobacco use (Brown et al. 2002, 2013), and there is initial evidence that distress intolerance may be greater among smokers with co-occurring pain (LaRowe et al. in press). There is also reason to suspect that other factors, such as experiential avoidance (Hayes et al. 1996), pain catastrophizing (e.g., Kosiba et al. 2018; Peters et al. 2005; Sullivan et al. 1995), emotion dysregulation (Johnson et al. 2012; Lumley et al. 2011) and anhedonia (e.g., Leventhal and Zvolensky 2015; Simons et al. 2014) may contribute to pain-smoking comorbidity.

In addition to identifying transdiagnostic factors, it is also worthwhile to consider the relative contributions of these constructs in the comorbidity of chronic pain and tobacco dependence. Although initial research has documented the unique contributions of pain-related fear and anxiety sensitivity in the context of pain treatment (Keogh et al. 2010), it is unclear how these factors may uniquely contribute to covariation between tobacco smoking and pain reporting. Future research should also determine the utility of targeting multiple transdiagnostic factors (vs. a single factor) within a single treatment protocol. For example, there is reason to believe that some effects of anxiety sensitivity occur via amplification of pain-related fear (e.g., Asmundson 1999). Thus, targeting pain-related fear may help to decrease pain and enhance smoking cessation outcomes, even in the absence of directly addressing anxiety sensitivity.

Finally, although most research to date has examined pain-related fear, the related construct of pain-related anxiety, and anxiety sensitivity as static traits, there is some evidence that these factors may operate in a more dynamic fashion. For example, previous work has detected within-person changes in anxiety sensitivity throughout a quit attempt (Assayag et al. 2012). These results further showed that pre- to post-treatment decreases in anxiety sensitivity were associated with a reduced risk of relapse. Indeed, additional research is warranted to examine the effects of within-person variability of pain-related fear and anxiety sensitivity

in pain and tobacco smoking, as such work could inform the conceptualization and testing of transdiagnostic treatments for tobacco smokers with comorbid pain.

Conclusions

We proposed a novel transdiagnostic conceptualization of pain-smoking comorbidity, in which pain-related fear and anxiety sensitivity are hypothesized to contribute to the onset and advancement of both tobacco cigarette smoking and chronic pain. This approach to understanding pain-smoking comorbidity has important implications for treatment, and future research should evaluate the utility of transdiagnostic intervention protocols for smokers with chronic pain. Future research should also work towards explicating the effects of pain-related fear and anxiety, as well as anxiety sensitivity in the co-occurrence of pain and smoking and attempt to identify other potentially transdiagnostic factors that may account for this highly prevalent and impactful comorbidity.

Compliance with Ethical Standards

Conflict of interest Lisa R. LaRowe, Michael J. Zvolensky, & Joseph W. Ditre declare that they have no conflict of interest.

Informed Consent Informed consent was obtained from all individual participants included in the study.

Human and Animal Rights This article does not contain any studies with human participants or animals performed by any of the authors.

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