

# Pain, Nicotine, and Smoking: Research Findings and Mechanistic Considerations

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Tobacco addiction and chronic pain represent 2 highly prevalent and comorbid conditions that engender substantial burdens upon individuals and systems. Interrelations between pain and smoking have been of clinical and empirical interest for decades, and research in this area has increased dramatically over the past 5 years. We conceptualize the interaction of pain and smoking as a prototypical example of the biopsychosocial model. Accordingly, we extrapolated from behavioral, cognitive, affective, biomedical, and social perspectives to propose causal mechanisms that may contribute to the observed comorbidity between these 2 conditions. The extant literature was 1st dichotomized into investigations of either *effects of smoking on pain* or *effects of pain on smoking*. We then integrated these findings to present a reciprocal model of pain and smoking that is hypothesized to interact in the manner of a positive feedback loop, resulting in greater pain and increased smoking. Finally, we proposed directions for future research and discussed clinical implications for smokers with comorbid pain disorders. We observed modest evidence that smoking may be a risk factor in the multifactorial etiology of some chronically painful conditions and that pain may come to serve as a potent motivator of smoking. We also found that whereas animal studies yielded consistent support for direct pain-inhibitory effects of nicotine and tobacco, results from human studies were much less consistent. Future research in the emerging area of pain and smoking has the potential to inform theoretical and clinical applications with respect to tobacco smoking, chronic pain, and their comorbid presentation.

**Keywords:** pain, nicotine, tobacco, smoking, chronic pain

Tobacco dependence and chronic pain represent two highly prevalent conditions that independently generate substantial challenges within the domains of psychology, medicine, public health, and economics, not to mention the personal toll exacted at an individual level. The high degree of comorbidity between pain and tobacco smoking has engendered additional burdens on patients and systems and has attracted the attention of researchers and clinicians within the medical and behavioral sciences. As illustrated in Figure 1, research on the topic of pain, nicotine, and tobacco smoking has increased dramatically in recent years. Indeed, approximately 40% of all of studies retrieved through PubMed ( $n = 74/185$ ) and PsycINFO ( $n = 51/118$ ) have been

published in only the past 5 years.<sup>1</sup> Thus, this would appear to be an opportune time to evaluate the literature to date.

This literature review begins with an overview of the problems of chronic pain and tobacco smoking in isolation, followed by a description of their comorbidity, noting possible third variables and confounds. The interaction of smoking and pain can be conceptualized as a prototypical example of the biopsychosocial model (Engel, 1977; Gatchel, Peng, Peters, Fuchs, & Turk, 2007), demonstrating the interplay between biomedical, behavioral, cognitive–affective, and physiological–sensory phenomena, all within a larger social context. Drawing from this perspective, the

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<sup>1</sup> Search terms used to retrieve studies from PubMed were *pain[majr] AND (smoking[majr] OR nicotine[majr] OR tobacco[majr]) NOT (cannabis OR marijuana OR angina)*. Search terms used to retrieve studies from PsycINFO were *pain AND (smoking OR nicotine OR tobacco) NOT (cannabis OR marijuana OR angina)*, with the terms *pain*, *smoking*, *nicotine*, and *tobacco* limited to keyword searches. Cannabis and marijuana were used as exclusionary terms to ensure the search was limited to tobacco smoking. The term *angina* was excluded because returned studies were likely an artifact of the PubMed indexing system and were not necessarily specific to the measurement of pain or pain-related variables, per se. For consistency, *angina* was subsequently excluded from the PsycINFO search, though this exclusion did not influence the number of studies returned.

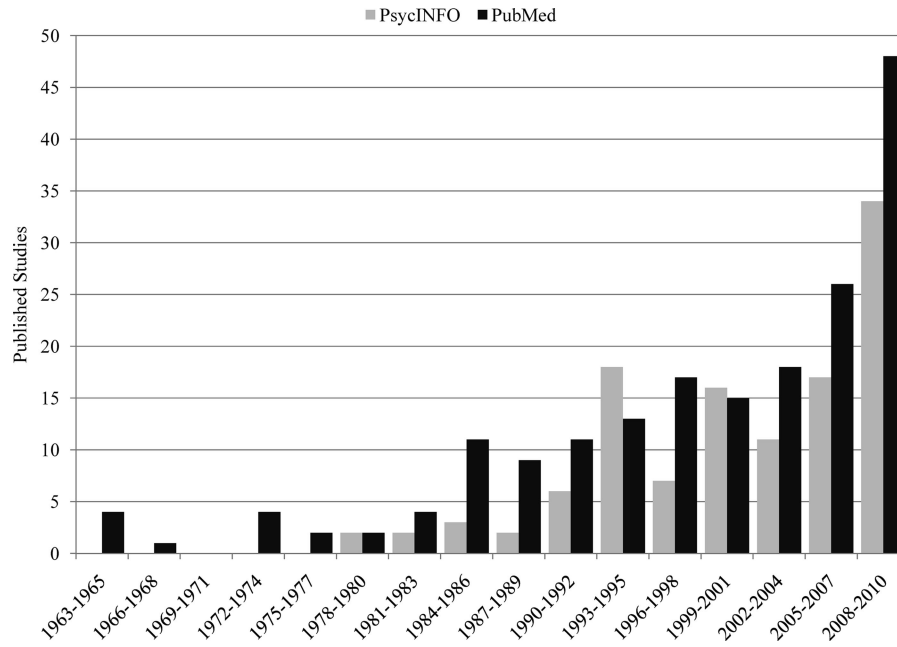


Figure 1. Number of published studies on pain, nicotine, and smoking from 1963 through 2010.

majority of this review addresses potential causal mechanisms that may contribute to the observed comorbidity between the two conditions. Cross-sectional, prospective, and experimental studies within the broad domain of pain and smoking can be usefully dichotomized, by direction of hypothesized causality, into investigations of either effects of smoking on pain or effects of pain on smoking. That is, there is a clear distinction to be made between studies that examine how smoking may serve as a risk factor for the development of chronic pain (i.e., effects of smoking on pain), relative to those that examine how pain may serve to increase smoking or maintain nicotine dependence (i.e., effects of pain on smoking). Accordingly, two sections of the current review are organized under these headings, respectively. We then integrate the extant literature to propose an integrative, reciprocal model of pain and smoking in which these two factors interact in the manner of a positive feedback loop, resulting in greater pain and increased smoking. Finally, we conclude with a discussion of directions for future research and clinical implications for smokers with comorbid pain disorders.

## Introduction to Pain and Smoking

### Acute and Chronic Pain

According to the International Association for the Study of Pain, pain is defined as “an unpleasant sensory and emotional experience associated with actual or potential tissue damage or described in terms of such damage” (International Association for the Study of Pain, 2008, p. 51). This definition acknowledges that pain is a multidimensional, subjective experience comprising sensory-physiological, motivational-affective, and cognitive-evaluative components (e.g., Melzack & Wall, 1965; Turk & Melzack, 2001). Pain motivates 50%–80% of all annual physician visits in the

United States (Mayo Clinic, 2001; Turk & Melzack, 1992). Although there has been little consensus regarding standard definitions (Harstall & Ospina, 2003), pain may be classified as acute, acute recurrent, chronic, chronic progressive, and laboratory induced (Turk & Melzack, 2011). The primary feature that has been used by researchers to distinguish acute from chronic pain is duration, with cutoffs occurring most often between 3 and 12 months following pain onset (Spanswick & Main, 2000; Thienhaus & Cole, 2002; Turk & Okifuji, 2001). Acute pain may be characterized by variable intensity and somatically focused distress and arousal (Turk & Melzack, 2001). In most cases, acute pain subsides following the removal of a noxious stimulus (e.g., experimentally induced pain) or treatment of an injury or disease (Lautenbacher & Fillingim, 2004).

Chronic (nonscanner related) pain is a critical national health problem with an annual economic impact of over \$125 billion in health care costs and lost productivity (American Pain Society, 2003; International Association for the Study of Pain, 2008). Although pain prevalence estimates derived from population-based surveys range as high as 64% (Hardt, Jacobsen, Goldberg, Nickel, & Buchwald, 2008; Stanford University Medical Center, 2005; Watkins, Wollan, Melton, & Yawn, 2008), the preponderance of data suggests that approximately 22%–30% of adults in the United States (or about 50–70 million people age 18 years and over) suffer from chronic pain (American Pain Society, 2003; Gallagher, 1999; Johannes, Le, Zhou, Johnston, & Dworkin, 2010; Portenoy, Ugarte, Fuller, & Haas, 2004). Variation in prevalence estimates are likely a function of how chronic pain is defined, the types of populations studied, and differences in survey methodology. According to the National Institutes of Health (PA-10-006), the deleterious effects of chronic pain have been demonstrated in morbidity, immune function, sleep, cognition, eating, mobility,

affective state, psychosocial behaviors, and overall functional status.

## Tobacco Smoking

Tobacco smoking remains the leading preventable cause of morbidity and mortality in the United States, accounting for approximately 443,000 deaths each year (Centers for Disease Control and Prevention [CDC], 2010a) and greater than \$190 billion in annual medical expenses and lost productivity (CDC, 2008a, 2008b). Despite known health consequences, an estimated 46 million people in the United States smoke cigarettes (CDC, 2010b). According to the CDC, 20.6% of U.S. adults were classified as current cigarette smokers in 2009, indicating that previous declines in smoking prevalence have stalled during the past 5 years (CDC, 2010b). In addition, approximately 88 million nonsmoking Americans are exposed to dangerous levels of secondhand smoke (CDC, 2010c). The recently updated U.S. Department of Health and Human Services' Clinical Practice Guidelines for Treating Tobacco Dependence (U.S. Department of Health and Human Services, 2008) identified smokers with comorbid medical conditions as important targets for treatment intervention. We have further proposed that some medical conditions and their associated symptoms (i.e., chronic and acute pain) might also serve to maintain tobacco dependence (Ditre & Brandon, 2008).

## Pain and Smoking

**Prevalence of smoking among persons in pain.** Pain and tobacco smoking have been linked in both the clinical and the empirical literature for decades, and recent epidemiological and clinical data indicate that the prevalence of smoking among persons in pain may be up to twice that observed in the general population. For example, in what may be the most comprehensive investigation of this topic to date, relations between chronic pain and cigarette smoking/nicotine dependence were examined with data from a nationally representative survey of 9,282 adults in the United States (Zvolensky, McMillan, Gonzalez, & Asmundson, 2009). Results indicated that the prevalence of current smoking was 42% among persons experiencing medically unexplained chronic pain in the past year, 35% among persons endorsing medically unexplained chronic pain in their lifetime, and 30% among persons endorsing past year or lifetime chronic neck or back pain. Furthermore, after adjusting for a host of highly relevant psychosocial factors (i.e., age, marital status, income, education, race, gender, and the presence of any lifetime mood, anxiety, or substance use disorder), persons who met criteria for past year nicotine dependence were almost twice as likely to endorse past year medically unexplained chronic pain (odds ratio [OR] = 1.83; 95% CI [1.15, 2.90]) and past year chronic neck or back pain (OR = 1.95; 95% CI [1.41, 2.68]). Similar prevalence rates and ORs that further substantiate the comorbidity of pain and smoking in nationally representative samples have been reported in Denmark (Ekholm, Gronbaek, Peuckmann, & Sjogren, 2009; Pisinger et al., 2011), Norway (Brage & Bjerkedal, 1996), Sweden (Hägg, Fritzell, & Nordwall, 2002; Jakobsson, 2008), Canada (Zvolensky, McMillan, Gonzalez, & Asmundson, 2010), and the United Kingdom (Palmer, Syddall, Cooper, & Coggon, 2003).

There is also evidence to suggest that the prevalence of smoking among persons in pain may be even greater among clinical pain

populations and those who endorse more severe pain-related functional impairment (e.g., treatment-seeking pain patients). For example, a cross-sectional analysis of a random sample of 250 treatment-seeking chronic pain patients revealed that 54% reported regular cigarette smoking (Jamison, Stetson, & Parris, 1991). This was greater than twice the 25.7% rate of smoking observed in the general population in 1991 (CDC, 1993). Furthermore, these smokers presented more maladaptive pain behaviors (i.e., decreased activity, increased medication reliance, and greater emotional distress) relative to treatment-seeking nonsmokers. More recently, 49% of 1,241 consecutive patients admitted to a 3-week outpatient pain-treatment program endorsed a history of regular smoking (Hooten, Shi, Gazelka, & Warner, 2011). Finally, of 145 consecutive pain patients seeking treatment at a hospital-based pain management center, 68% identified as current smokers (Michna et al., 2004). Notably, these patients presented with significant pain (average pain rating of 7 out of 10), and they were prescribed opioid medications for pain management.

**Population base rates.** Although there is evidence to support the notion that tobacco smokers are overrepresented among persons in pain relative to the general population, a brief consideration of population base rates is warranted. In its simplest form, a base rate is the prevalence of some construct or condition (numerator) within a population (denominator). Complication arises when one considers that a numerator can include combinations of factors and that parameters defining a population are subject to considerable variation (McCaffrey, Duff, & Westervelt, 2000). The ultimate base rates of tobacco smoking among persons with chronic pain (or chronic pain among persons who smoke) are extremely difficult to quantify because they are highly dependent on operational definitions of chronic pain (for which there is little consensus), the setting from which the population was derived (e.g., chronic pain treatment program vs. community-based smoking cessation clinic), essential features of the painful condition (e.g., location, duration, severity, and degree of functional impairment), and smoking-relevant variables (e.g., current smoking status, history of smoking). Whereas some researchers have suggested that the quantification of such parameters pose insurmountable challenges (Miettinen & Caro, 1994), others concluded that the most appropriate base rate information would be derived from epidemiological, clinical, or setting-specific samples (Elwood, 1993). For the purpose of the current review, we endorse the latter approach. Given that both pain and smoking are highly prevalent conditions, it seems reasonable to conclude that their comorbidity would likely be of clinical and public health significance across a variety of contexts, if not in all of them.

**Sociodemographic factors and potential confounds.** Consideration of confounding or third variables is critical in determining the extent to which causal inferences can be drawn from study findings (T. D. Cook & Campbell, 1979). Sociodemographic population data may also be as relevant as other denominator data when evaluating prevalence rates for comorbid disorders. Throughout our review of the literature on pain and smoking, we noted that although most studies incorporated some form of statistical control for common sociodemographic factors (e.g., age, gender, activity level, body mass index [BMI], education, income, and occupational variables), there was substantial variation in the number of covariates included across studies. We also noted that few individual studies assessed or controlled for other potential

confounds that are prevalent among both smokers and persons in pain (e.g., comorbid medical and psychiatric conditions). The omission of such variables may reduce confidence in study findings, partly depending on level of analysis (e.g., between- vs. within-subjects), with between-subjects designs being especially susceptible to the influence of important individual difference factors. However, more recent population-based surveys and meta-analyses have demonstrated effects above and beyond the influence of sociodemographic factors and comorbid medical and psychiatric disorders (Shiri, Karppinen, Leino-Arjas, Solovieva, & Viikari-Juntura, 2010; Sugiyama et al., 2010; Zvolensky et al., 2009, 2010). To further underscore the relevance of psychiatric comorbidity as a third variable of potentially causal import, we briefly review several disorders that are most prevalent among smokers and persons in pain.

#### **Psychiatric comorbidity.**

**Mood disorders.** Symptoms of depression and anxiety are more prevalent among both smokers (Breslau, 1995; Williams & Ziedonis, 2004) and persons with chronic pain (Arnou et al., 2006; Atkinson, Slater, Patterson, Grant, & Garfin, 1991; Dersh, Polatin, & Gatchel, 2002), often doubling rates observed in the general population. There is also some evidence that symptoms of depression/anxiety and smoking behavior may be reciprocal in nature (e.g., Boden, Fergusson, & Horwood, 2010; Jamal, Van der Does, Penninx, & Cuijpers, 2011; J. G. Johnson et al., 2000; Morrell & Cohen, 2006). The role of depression is of particular interest because chronic pain patients who smoke tobacco have consistently been shown to endorse greater levels of depression when compared with their nonsmoking counterparts (Hooten, Shi, et al., 2011; Hooten et al., 2009; Vogt, Hanscom, Lauerman, & Kang, 2002; Weingarten et al., 2008; Weingarten, Podduturu, et al., 2009). Smokers in pain have also been shown to endorse greater levels of suicidal ideation (Fishbain, Lewis, Gao, Cole, & Rosomoff, 2009), affective distress, and pain-related anxiety (Hooten et al., 2009). Interrelations between pain, smoking, and comorbid mood disorders are likely complex, and they will require substantial empirical scrutiny before any direction of causality can be suggested or inferred.

**Substance use disorders.** Tobacco smoking has been associated with an increased prevalence of alcohol and substance use disorders (Barrett, Tichauer, Leyton, & Pihl, 2006; Breslau, Kilbey, & Andreski, 1991), and smokers may account for up to 80% of persons who misuse drugs and alcohol (Hurt et al., 1996; Kalman, Morissette, & George, 2005; Romberger & Grant, 2004). Chronic pain patients also appear more likely to present with comorbid substance use and dependence disorders, though these estimates vary considerably across studies (Fishbain, Rosomoff, & Rosomoff, 1992; Hoffmann, Olofsson, Salen, & Wickstrom, 1995; Manchikanti et al., 2006; Manchikanti, Pampati, Damron, Beyer, & Barnhill, 2003). Among a recent sample of individuals with chronic back pain (Fishbain et al., 2007), smokers (relative to nonsmokers) were more likely to endorse current use of alcohol (71% vs. 29%), cannabis (77% vs. 23%), amphetamines (86% vs. 14%), and cocaine (70% vs. 30%). It is important to note, however, that the cross-sectional nature of these findings prohibit conclusions regarding the temporal onset of smoking, substance misuse, and chronic pain. For example, up to 18% of veterans with spinal cord injury could not recall whether their substance abuse/

dependence problems began before or after their injury occurred (Ditre & Radnitz, 2005).

**Personality disorders.** Meta-analytic and longitudinal studies have provided convergent evidence that individual differences in the personality domains of extraversion and neuroticism represent important risk factors for smoking initiation and maintenance (Munafò & Black, 2007; Munafò, Zetteler, & Clark, 2007). In general, personality disorders have been associated with substance use and mood disorders, which in turn have been associated with tobacco smoking (Frosch, Shoptaw, Nahom, & Jarvik, 2000). Maladaptive personality traits (e.g., neuroticism, hypochondriasis, and hysteria) are also more common among persons with chronic pain relative to the general population (Dersh et al., 2002; Fillinim, 2005; Weisberg, Keefe, Gatchel, & Turk, 1999). Interestingly, neuroticism has been positively associated with affective dimensions of pain (Wade, Dougherty, Hart, Raffi, & Price, 1992), the use of passive coping strategies, and pain intensity (Ramírez-Maestre, Lopez Martinez, & Zarazaga, 2004), whereas extraversion has been positively associated with the use of active coping strategies and negatively related to perceived pain intensity (Ramírez-Maestre et al., 2004). To date, only one study has examined associations between pain, smoking, and personality (Fishbain et al., 2007), and results indicated that a greater percentage of smoking chronic pain patients endorsed criteria for histrionic personality disorder (62% vs. 38%) than did nonsmoking chronic pain patients.

**Social environmental factors.** Consistent with the biopsychosocial perspective, psychological and physiological processes are influenced by, and can subsequently influence, an organism's social environment. Social environmental factors (e.g., social support, family environment, occupational functioning, access to health care, education, socioeconomic status, social policy) play an important role in the cause, course, and outcomes of both pain and smoking (Gatchel et al., 2007). For example, condition-specific trajectories (e.g., initiation and maintenance of both pain and smoking) have consistently been associated with the quality of perceived social support and interpersonal relationships (e.g., Ennett et al., 2010; Keefe, Dunsmore, & Burnett, 1992; Mermelstein, Cohen, Lichtenstein, Baer, & Kamarck, 1986; Osborne, Jensen, Ehde, Hanley, & Kraft, 2007). Lower socioeconomic status and educational attainment have also been independently associated with greater pain and increased cigarette consumption (Dionne et al., 2001; Galea, Nandi, & Vlahov, 2004; Klaber Moffett, Underwood, & Gardiner, 2009). Similarly, reduced access to frontline treatments for smoking cessation (i.e., counseling and pharmacotherapy) and pain (i.e., multidisciplinary intervention) have been associated with poorer outcomes for both conditions (U.S. Department of Health and Human Services, 2008; Guzmán et al., 2001). Among smokers, social policy factors (e.g., smoking prohibitions, increased taxation of cigarettes) have been shown to decrease cigarette consumption (Fichtenberg & Glantz, 2002). Finally, it is important to note the bidirectional relationship between health and social environmental factors. For example, chronic pain has been associated with adverse social outcomes (e.g., unemployment and social isolation), as well as changing roles and functional disposition in occupational, recreational, and social/familial contexts (e.g., Braden, Zhang, Zimmerman, & Sullivan, 2008; Closs, 2009; Kerns, Turk, & Rudy, 1985). Likewise, smokers are increasingly



relegated to the periphery of their social networks (Christakis & Fowler, 2008).

### Effects of Smoking on Pain

#### Smoking as a Risk Factor for Chronic Pain

Chronic pain can be viewed as an ongoing, multifactorial process in which reciprocal interactions between numerous biopsychosocial factors determine the subjective experience and patient response (Turk & Monarch, 2002). Accordingly, the multifactorial etiology of specific chronic pain conditions should be considered when interpreting findings, as most causal factors are likely to demonstrate relatively weak effects (Buchanan, Weiss, & Fullerton, 2006). Within this conceptual framework, even modest predictive effects can have clinical significance. Also, it is important to consider that the extent to which any causal determinations can be inferred is largely a function of (a) evidence of covariation between the posited cause and effect, (b) temporal precedence of the cause, and (c) the degree to which plausible alternative explanations have been excluded (T. D. Cook & Campbell, 1979). Therefore, throughout the sections that follow, greater emphasis was placed on studies that statistically controlled for potential confounds and/or demonstrated temporal precedence (e.g., prospective, cohort studies).

**Low back pain.** Many studies have examined associations between smoking status (i.e., never, former, current) and chronic low back pain (LBP), and the authors of several reviews concluded that smoking should be considered a risk factor for the incidence and prevalence of LBP (Goldberg, Scott, & Mayo, 2000; Leboeuf-Yde, 1995, 1999). Most recently, however, the authors of a seminal meta-analysis on this topic concluded that both current and former smokers have a higher prevalence and incidence of LBP than do never smokers (Shiri et al., 2010).

Shiri et al. (2010) conducted separate meta-analyses for cross-sectional ( $N = 27$ ) and prospective cohort studies ( $N = 13$ ). Among cross-sectional studies, current smoking was associated with increased prevalence of past month LBP (OR = 1.30, 95% CI [1.16, 1.45]), past year LBP (OR = 1.33, 95% CI [1.26, 1.41]), seeking treatment for LBP (OR = 1.49, 95% CI [1.38, 1.60]), chronic LBP (OR = 1.79, 95% CI [1.27, 2.50]), and disabling LBP (OR = 2.14, 95% CI [1.11, 4.13]). Thus, it appears that the association between current smoking and LBP increased as a function of LBP severity and functional impairment. Among prospective studies, both former (OR = 1.32, 95% CI [0.99, 1.77]) and current (OR = 1.31, 95% CI [1.11, 1.55]) smokers had an increased incidence of LBP relative to never smokers. Both cross-sectional and prospective studies also demonstrated evidence of a dose-response relation between number of cigarettes smoked per day and LBP. Importantly, the majority of studies included in these meta-analyses (particularly the prospective studies) statistically controlled for a variety of potential confounds (e.g., age, gender, BMI, physical activity, comorbid health disorders, co-occurring substance misuse, and psychiatric comorbidity).

**Possible mechanisms.** The most widely accepted explanation for the association between smoking and LBP is disc degeneration via malnutrition of spinal disc cells by carboxy-hemoglobin-induced anoxia or vascular disease (Akmal et al., 2004). Smoking introduces a variety of toxic substances (e.g., carbon monoxide)

that may damage the interior lining of blood vessels, thus decreasing their capacity to carry oxygen, leading to tissue starvation, degeneration, and death (Rahman & Laher, 2007). There is also some evidence that nicotine may accelerate intervertebral disc degeneration by instigating cell damage in both the nucleus pulposus and annulus fibrosus (Sørensen et al., 2009) and/or influencing the metabolism of the intervertebral disc (Battié et al., 1995; Holm & Nachemson, 1988). Indeed, nicotine has been shown to induce serum proteolytic enzyme activity (Fogelholm & Alho, 2001). Furthermore, smoking has consistently been demonstrated to induce intervertebral disc degeneration in animal models (Iwahashi, Matsuzaki, Tokuhashi, Wakabayashi, & Uematsu, 2002; Nemoto et al., 2006; Oda et al., 2004; Uematsu, Matuzaki, & Iwahashi, 2001), possibly preceded by changes in gene expression (Uei et al., 2006). Also, disc degeneration among cigarette smokers appears to be more severe than disc degeneration observed in nonsmokers (Fogelholm & Alho, 2001). There is, however, reason to believe that smoking-induced intervertebral disc degeneration may be repaired by cessation of smoking (Nemoto et al., 2006). Finally, smoking has been hypothesized to accelerate bone loss, resulting in alterations of bone microarchitecture, leading to vertebral deformities and loss of spinal stability (Hansson & Roos, 1981; Seeman, 1996).

**Rheumatoid arthritis.** Rheumatoid arthritis (RA) is a chronic inflammatory disease that causes progressive joint destruction and leads to restricted activities of daily living and a deteriorating quality of life. Unfortunately, persistent and disabling pain is also a prominent feature of RA (Edwards, Calahan, Mensing, Smith, & Haythornthwaite, 2011; Woolf & Pfleger, 2003). Although a relationship between smoking and RA has been reported for over 20 years (Vessey, Villard-Mackintosh, & Yeates, 1987), only recently has smoking been studied as a potential pathogenetic agent in RA. Today, smoking is considered to be the best established environmental risk factor for the development of RA (e.g., Aho & Heliövaara, 2004; Costenbader, Feskanich, Mandl, & Karlson, 2006; Finckh, Dehler, Costenbader, & Gabay, 2007; Sugiyama et al., 2010). The authors of a comprehensive review conducted in 2001 concluded that modest evidence of an association between smoking and the incidence/severity of RA cannot be overlooked and that smoking appears to have a "strong causal connection to rheumatoid vasculitis," which is a complication of longstanding, severe RA (Albano, Santana-Sahagun, & Weisman, 2001, p. 146). Most recently, the authors of a seminal meta-analysis on smoking and RA concluded that smoking is "clearly" a risk factor for the development of RA (Sugiyama et al., 2010). Specifically, they found that the odds of developing RA was approximately two times greater for male smokers (OR = 1.89, 95% CI [1.56, 2.28]) and 1.27 (95% CI [1.12, 1.44]) times greater for female smokers, relative to nonsmokers. Furthermore, there was a nearly fourfold risk of developing RA among currently smoking, rheumatoid factor (RF)-positive men (OR = 3.91, 95% CI [2.78, 5.50]).

Smoking may also influence RA disease severity, possibly in a dose-dependent fashion (Albano et al., 2001; Harrison & Silman, 2000; Masdottir et al., 2000; Matvey et al., 2002; Papadopoulos et al., 2005; Saag et al., 1997; Soderlin, Petersson, Bergman, & Svensson, 2011; Wolfe, 2000), though not all studies have found smoking to accelerate RA disease progression (Finckh et al., 2007). After controlling for sociodemographic variables (age, sex,

BMI, marital status, education, and income), Saag et al. (1997) found smoking to be associated with multiple markers of RA disease severity, including RF (OR = 3.06, 95% CI [1.67, 5.59]) and radiographic erosions (OR = 2.37, 95% CI [1.23, 4.56]). Similarly, Papadopoulos et al. (2005) demonstrated an association between a history of heavy smoking and increased odds of radiological damage (OR = 2.5, 95% CI [1.6, 3.5]). Smoking may also reduce the efficacy of RA treatments, including tumor necrosis factor (TNF) antagonists (Mattey, Brownfield, & Dawes, 2009) and disease-modifying antirheumatic drug (DMARD) therapy (Harty & Veale, 2010). Though it seems likely that smoking would interact with genetic risk in the development of RA (Criswell et al., 2006), smoking and genetic predisposition may be independent risk factors in the development of RA, with smoking causing earlier disease expression in patients without a genetic predisposition (Hutchinson, Shepstone, Moots, Lear, & Lynch, 2001).

**Possible mechanisms.** Potential smoking-RA mechanisms are currently being examined (Klareskog, Padyukov, & Alfredsson, 2007), and several possibilities have been suggested. In a recent review of risk factors for RA development, the authors concluded that smoking acts synergistically with other RA risk factors, including immunoglobulin M–RF (IgM–RF), anti-cyclic citrullinated peptide antibodies (anti-CCP), and shared epitopes (Christensen, Lindegaard, & Junker, 2008). Similar associations have been found among African Americans with RA (Mikuls et al., 2008). RF is the most salient prognostic marker for RA severity, and several studies indicate that smokers maintain higher concentrations of serum RF (Masdottir et al., 2000; Papadopoulos et al., 2005; Saag et al., 1997). Thus, increased RF may partially mediate the relationship between smoking and more severe disease expression (Sugiyama et al., 2010; Tuomi, Heliovaara, Palosuo, & Aho, 1990; Wolfe, 2000). It has also been hypothesized that known associations between smoking and the development of urinary tract infections (UTIs) and the link between number of UTIs and the development of RA might explain some of the increased frequency of RA among smokers (Rashid & Ebringer, 2008). Finally, it has been suggested that cigarette smoking might increase basal metabolic rate (BMR), the principal indicator of human metabolism and its abnormalities, leading to poorer disease outcomes among individuals with RA because of hypercatabolism caused by systemic inflammation (Metsios et al., 2008).

**Headache pain.** Recent research has identified a strong association between tobacco smoking and the prevalence of headache pain (Aamodt, Stovner, Hagen, Brathen, & Zwart, 2006; Beck, Sieber, & Trejo, 2005; Ghandour, Overpeck, Huang, Kogan, & Scheidt, 2004; Waldie, McGee, Reeder, & Poulton, 2008). For example, a population-based survey ( $N = 51,383$ ) revealed that smokers were 1.5 times (95% CI [1.3, 1.6]) more likely to report headaches than were never smokers, after controlling for sex, age, and education (Aamodt et al., 2006). Smokers in this sample were also 1.7 times more likely (95% CI [1.3, 2.2]) to endorse experiencing headache activity on more than 14 days per month. These results were supported by two prospective studies, the first of which revealed that both smoking status and nicotine content of the preferred cigarette adversely influenced headache activity, with smokers reporting greater weekly peak headache intensity than nonsmokers (Payne et al., 1991). Participants in a more recent longitudinal study were asked about their cigarette smoking and headache activity at ages 11 years, 13 years, 15 years, and 26 years

(Waldie et al., 2008). Results of cross-sectional analyses indicated that the likelihood of frequent headaches during midadolescence doubled for smokers relative to nonsmokers (OR = 2.05, 95% CI [1.31, 3.31]), even after adjusting for gender and family socioeconomic status.

**Cluster headache.** A more severe and potentially chronic form of headache, cluster headache, typically causes extreme pain of a piercing quality near one eye or temple that lasts for between 15 min and 3 hr. Results of multiple investigations indicate that 80%–90% of all cluster headache patients have a significant history of smoking tobacco (Rozen, 2001; Rozen, Niknam, Shechter, Young, & Silberstein, 2001; Schürks & Diener, 2008; Torelli, Cologno, & Manzoni, 1999). There is also evidence that initiation of smoking behavior usually occurs prior to the onset of cluster headaches for both men ( $M$  age = 31.3 years,  $SD = 13.5$ ) and women ( $M$  age = 29.4 years,  $SD = 15.9$ ), providing some indication of temporal precedence and suggesting that smoking may prime the inception of cluster headache activity (Rozen et al., 2001). Although the importance of smoking in the temporal etiology of cluster headaches remains unclear, recent studies suggest that prolonged exposure to secondhand smoke may also play a causal role in its development (Rozen, 2005, 2010). Indeed, data from the United States Cluster Headache survey indicate that 61% of never smokers with cluster headaches were raised in a household with at least one parent who smoked (Rozen, 2010).

**Possible mechanisms.** It has been suggested that frequent exposure to nicotine and other chemicals found in tobacco smoke may precipitate headache activity by increasing the sensitivity of pain receptors in the brain, thus modulating the neurological processing of sensory information (Waldie et al., 2008). Aamodt et al. (2006) took these considerations a step further by noting several effects of smoking that might also induce headache activity, including changes in levels of nitric oxide in the brain, carbon monoxide-induced anoxia, decreased monoamine oxidase (MAO) activity, and a reduction in the efficacy of common headache medications because they may be metabolized more quickly by smokers.

**Oral pain.** Tobacco use is a known risk factor for the onset and exacerbation of painful oral diseases (G. K. Johnson & Slach, 2001; Kinane & Chestnutt, 2000; Winn, 2001), and associations between smoking and increased tooth sensitivity have been reported (Al-Wahadni & Linden, 2002; Millar & Locker, 2007; Rees & Addy, 2002). For example, one study showed current smoking to be associated with a 30% greater chance of experiencing tooth pain, after accounting for gender, education, occupation, general health condition, and dental care utilization/fear (Unell, Soderfeldt, Halling, & Birkhed, 1999). The results of another analysis, designed to explore the association between smoking and oral pain at the onset of a longitudinal study of oral health ( $N = 873$ ), found that current smoking (relative to never smoking) increased the odds of experiencing oral pain (OR = 1.5, 95% CI [1.2, 2.6]) and pain-related impacts such as trouble sleeping (OR = 2.0, 95% CI [1.2, 3.5]) and activity reduction (OR = 2.1, 95% CI [1.3, 3.5]), after adjusting for age, gender, race, education, oral hygiene, and dental care (Riley, Tomar, & Gilbert, 2004). Moreover, current smokers in this study reported experiencing greater tooth and gum pain than did former (OR = 2.1, 95% CI [1.3, 3.7]) or never smokers (OR = 1.5, 95% CI [1.2, 2.6]), after controlling for the

same confounds, suggesting that smoking cessation may decrease the odds of experiencing pain associated with oral disease.

**Possible mechanisms.** Potential mechanistic factors that may underlie the observed relations between oral pain and smoking include reduced salivary flow, progressive tooth decay, poor wound healing, and periodontal disease-associated exposure of root surfaces (Riley et al., 2004). Riley et al. (2004) also suggested that exposure to tobacco smoke may increase pain sensitivity within the oral cavity, though such studies have yet to be conducted.

**Other painful conditions associated with smoking.** In addition to those reviewed herein, there is evidence of associations between tobacco smoking and the prevalence/severity of several other painful conditions, including: fibromyalgia (Lee et al., 2011; Weingarten, Podduturu, et al., 2009; Wolfe & Hawley, 1998; Yunus, Arslan, & Aldag, 2002), dyspepsia (Wildner-Christensen, Hansen, & De Muckadell, 2006), menstrual pain (Allen, Hatsukami, Christianson, & Brown, 2000; Gold et al., 2007), pregnancy-related pelvic pain (Biering, Aagaard Nohr, Olsen, Nybo Andersen, & Juhl, 2010), Buerger's disease (Quintas & Albuquerque, 2008), HIV-related bodily pain (Patel et al., 2006; Turner et al., 2001), painful temporomandibular joint disorders (Melis et al., 2010; Weingarten, Iverson, et al., 2009), pain associated with osteoarthritis (Amin et al., 2007), and sickle cell disease (Cohen, DeBaun, Blinder, Strunk, & Field, 2010).

**Summary and conclusions.** Copious numbers of studies provide evidence of substantial covariation between tobacco smoking and the prevalence of several chronically painful conditions. Most of the studies emphasized within this review made some attempt to assess and statistically control for potential confounds, with the majority focusing on sociodemographic variables. Future investigations of interrelations between pain and smoking would benefit from consistently accounting for a variety of factors that are highly prevalent among smokers and persons with chronic pain (e.g., comorbid medical and psychiatric disorders). Future studies would also benefit from examining smoking status in greater detail (e.g., current vs. former vs. never smokers) and with respect to continuous smoking-related variables (e.g., average daily cigarette consumption, number of years smoking, number of years since quitting, and nicotine dependence).

In terms of tobacco smoking as a risk factor in the etiology of chronic pain, causal evidence is limited. Most researchers and clinicians would agree that a causal association between smoking and chronic pain could not be established via randomized controlled trials with humans due to obvious ethical limitations. However, well-designed prospective cohort studies are more than capable of establishing temporal precedence in the assessment of causality. To date, there is modest evidence to support a causal role of tobacco smoking in the development of chronic LBP (e.g., Shiri et al., 2010). This conclusion is largely based on the number of prospective studies considered and the broad range of potential third variables accounted for. Indeed, most chronic conditions of multifactorial etiology would likely demonstrate modest causal effects at the individual factor level (Buchanan et al., 2006). There is also evidence of a causal relation between smoking and the development of RA (e.g., Sugiyama et al., 2010). Approximately 30% of the articles included in the meta-analysis by Sugiyama et al. (2010) were prospective cohort studies, and they examined an assortment of potential confounds implicated in the development

and progression of RA (e.g., age, social class, BMI, education, coffee consumption, and menopause status).

Perhaps it should be of little surprise that nascent support for a causal role of tobacco smoking has been observed among chronically painful conditions that have received the most empirical attention (e.g., LBP, RA), thus providing the data necessary to conduct meta-analyses. To better elucidate causality, rule out the influence of third variables, and reveal mechanisms underlying associations between pain and smoking, additional prospective studies (designed and powered to detect mediating and moderating factors) are clearly warranted. It is also important to consider the possibility that relations between tobacco smoking and the development of chronic pain may not apply to the same degree for all conditions. For example, smoking-related associations may vary as function of condition-specific etiology, severity, operational definition, and the extent to which there are known pathological mechanisms. They may also vary as function of individual differentiation in the pharmacological effects of smoking, the role of nicotine versus other constituents found in tobacco smoke, and the degree to which persons with limited tolerance for pain may be more likely to initiate and maintain smoking behavior.

### Acute Effects of Smoking and Nicotine on Pain

Although there is initial evidence to support tobacco smoking as a risk factor for some types of chronic pain, there is also somewhat paradoxical evidence to suggest that nicotine may have short-acting analgesic effects. In contrast to the studies reviewed thus far, investigations of potential pain-inhibitory effects of nicotine and tobacco have been predominantly experimental (i.e., laboratory-based) in nature. Experimental pain models allow for standardization of the painful stimulus, systematic manipulation of relevant variables, and reliable measurement of the pain response (Edens & Gil, 1995). Laboratory-based studies in the area of pain and smoking have primarily focused on how nicotine (delivered directly or via tobacco smoke) might modulate pain responding among both animals and humans.

**Animal models.** Direct pain-inhibitory effects of nicotine and tobacco smoke have consistently been demonstrated in animal studies over 3 decades (e.g., Rowley, Payappilly, Lu, & Flood, 2008; Sahley & Berntson, 1979). Some of the most commonly utilized methods for testing antinociceptive effects of nicotine within rodent samples have incorporated either thermal (e.g., hot plate, tail flick) or pressure-based (i.e., mechanical stimulation) models of experimental pain induction. There is also variation in how nicotine is administered across animal studies, including both direct (e.g., nicotine delivered subcutaneously) and indirect (e.g., nicotine delivered via tobacco smoke) methods. Pain-inhibitory effects of nicotine have been hypothesized to differ across models to the extent that they may engage different spinal and supraspinal pathways (Shi, Weingarten, Mantilla, Hooten, & Warner, 2010).

In the hot plate model, the animal is placed on a glass surface that is heated, and pain threshold is measured in terms of latency to jump or retract a paw. In the tail flick model, the animal is restrained with its tail positioned over a heat source and pain threshold is measured as a function of latency to move its tail away from the heat source. In the pressure based model, a von Frey instrument is applied to the animal's paw, and pressure tolerance



is measured as the amount of force with which the von Frey instrument was applied at the moment of paw withdrawal.

Antinociceptive effects of nicotine delivered subcutaneously have been demonstrated in both hot plate and tail flick models, with animals that received nicotine demonstrating increased latency to withdrawal from the heat stimulus (Aceto, Bagley, Dewey, Fu, & Martin, 1986; Anderson et al., 2004; Block, Chin, Wu, & Zbuzek, 1993; Carstens, Anderson, Simons, Carstens, & Jinks, 2001; Rowley et al., 2008; Tripathi, Martin, & Aceto, 1982). Pain-inhibitory effects are also evident when applying pressure-based mechanical stimulation of a paw incision (Rowley & Flood, 2008) and in tail flick models when nicotine is administered via cigarette smoke in an environmental chamber (Anderson et al., 2004; Simons et al., 2005). There is also evidence of a positive dose-response effect between quantity of nicotine administered and increased latency to withdraw, with maximum latency reaching approximately double that observed at baseline (Aceto et al., 1986; Rowley et al., 2008). Finally, in contrast to acute antinociceptive effects, it appears that chronic exposure to both subcutaneous nicotine and tobacco smoke may result in nicotine tolerance and reduced pain inhibition (Anderson et al., 2004; Carstens et al., 2001; Galeote, Kieffer, Maldonado, & Berrendero, 2006; Simons et al., 2005), possibly mediated by changes in the endogenous opioid system (Shi et al., 2010).

**Human studies.** A total of 18 experimental studies designed to test the analgesic effects of nicotine or tobacco smoke in human populations were identified through systematic literature searches conducted with PsycINFO and PubMed databases. Search criteria were limited to human samples, and major search terms included *pain AND (smoking OR nicotine OR tobacco)*. The methodological designs of returned records were reviewed by two independent raters. All studies that did not utilize experimental pain induction or reported outcome variables reflecting indices other than pain threshold or tolerance were excluded. Citations and reference sections of included articles were cross-referenced to ensure accuracy and completeness. Sample composition (e.g., smokers vs. nonsmokers), method of experimental pain induction, experimental conditions/manipulations (e.g., method of nicotine delivery, inclusion of deprived smokers), and primary findings were recorded for each study (see Tables 1 and 2).

Of 18 studies examining the acute effects of nicotine and tobacco on pain perception, 56% ( $N = 10$ ) revealed evidence of pain inhibition (Fertig, Pomerleau, & Sanders, 1986; Jamner, Girdler, Shapiro, & Jarvik, 1998; Kanarek & Carrington, 2004; Lane, Lefebvre, Rose, & Keefe, 1995; Nastase, Ioan, Braga, Zagrean, & Moldovan, 2007; Nesbitt, 1973; Pauli, Rau, Zhuang, Brody, & Birbaumer, 1993; Perkins, Grobe, Stiller, & Scierka, 1994; O. F. Pomerleau, Turk, & Fertig, 1984; Silverstein, 1982). There were, however, a significant number of studies with similar methodologies ( $N = 8$ ) that failed to observe nicotine- or smoking-related antinociception (Jarvik, Caskey, Rose, Herskovic, & Sadeghpour, 1989; Knott, 1990; Knott & De Lugt, 1991; Muser, Waller, Levander, & Schalling, 1984; Shiffman & Jarvik, 1984; Sult & Moss, 1986; Unrod, Kassel, & Robinson, 2004; Waller, Schalling, Levander, & Edman, 1983). Tables 1 and 2 provide a comparison of representative studies that observed pain-inhibitory effects of nicotine or tobacco (see Table 1) with those that did not (see Table 2). Interestingly, only Nesbitt (1973) used a procedure in which participants were required to smoke during pain induction.

Three studies showed evidence of a dose-response effect, with increased pain threshold and/or tolerance observed for cigarettes and nasal spray containing greater amounts of nicotine (Nesbitt, 1973; Perkins et al., 1994; Silverstein, 1982). There were also some data to suggest that pain threshold might represent a more accurate measure of the antinociceptive effects of nicotine from smoking than pain tolerance (O. F. Pomerleau et al., 1984). Finally, more recent investigations indicated that the pain-inhibitory effects of smoking may be augmented by consuming either caffeine or sucrose (Kanarek & Carrington, 2004; Nastase et al., 2007).

In addition to examinations of the acute effects of nicotine or smoking on pain perception, the results of some studies indicate that smoking status may be related to pain responding, with current smokers exhibiting reduced pain sensitivity when compared with nonsmokers (e.g., Girdler et al., 2005; Jamner et al., 1998; Nesbitt, 1973; Silverstein, 1982). Girdler et al. (2005) further demonstrated that smoking status-related analgesia may be moderated by gender, subjective stress, and pain modality, such that female smokers had greater threshold and tolerance times to ischemic pain than did female nonsmokers when pain testing followed rest, and male smokers had greater threshold and tolerance to cold pressor pain than did male nonsmokers after both rest and stress. These authors speculated that evidence of reduced pain perception in smokers, along with an absence of observed interrelationships between endogenous pain regulatory mechanisms and pain sensitivity, might reflect a maladaptive response to chronic smoking (Girdler et al., 2005). Relationships between smoking status and increased tolerance for pain have not, however, been demonstrated in all studies (i.e., Perkins et al., 1994).

Mixed evidence for smoking-related analgesia in humans may stem from nicotine dosing, gender differences, the stimuli used to induce experimental pain, and the possibility that the antinociceptive effects of smoking may be achieved indirectly via other mediating psychological or physiological factors (Girdler et al., 2005; Jamner et al., 1998; Kanarek & Carrington, 2004; O. F. Pomerleau et al., 1984; Shiffman & Jarvik, 1984; Unrod et al., 2004), as discussed below.

#### Possible mechanisms.

**Nicotinic acetylcholine receptors (nAChRs).** There is a general consensus that pain-inhibitory effects of nicotine and tobacco likely involve the activation of nicotinic acetylcholine receptors (nAChRs). Nicotinic cholinergic receptors can be found in the central nervous system, autonomic ganglia, the neuromuscular junction, and several nonneuronal tissues (Benowitz, 2008b). Nicotine may produce central antinociceptive effects by agonizing nAChRs in the brainstem (Gao et al., 2010), particularly the  $\alpha 4\beta 2$  subtype (Damaj et al., 2007), resulting in the activation of spinal cord descending pain-inhibitory pathways (Christensen & Smith, 1990). In fact, some researchers believe that nAChR agonists may give rise to a new class of analgesics (Bunnelle, Dart, & Schimpf, 2004; Bunnelle & Decker, 2003; Decker, Rueter, & Bitner, 2004). Support for nAChR activation as at least a partial mediator of nicotine- and tobacco-induced pain reduction is best illustrated by animal studies of epibatidine, a potent but nonselective nAChR agonist (Daly et al., 2000). Epibatidine, an alkaloid isolated from the skin of a poisonous frog indigenous to Ecuador, has analgesic effects that are several hundred times more potent than morphine (Damaj et al., 1998; Okabe & Natsume, 1994; Rupniak et al.,



Table 1  
*Acute Effects of Nicotine and Tobacco on Pain Perception: Pain-Inhibitory Effects Observed*

Study	Participants	Pain	Conditions	Threshold	Tolerance	Primary findings
Nesbitt (1973)	30 sm; 30 ns	Electrical	High-nic cigarette Low-nic cigarette Sham smoke	Unspecified	20.8 shocks 18.6 shocks 15.9 shocks	Tolerance increased as a function of nicotine dose in sm, but not in ns. High-nic: sm = 24.5; ns = 17.0. Low-nic: sm = 19.0; ns = 18.2. Sham smoke: sm = 13.0; ns = 18.8.
Silverstein (1982)	30 sm; 10 ns	Electrical	High-nic cigarette Low-nic cigarette Deprived	14.2 shocks 6.9 shocks 6.3 shocks	20.6 shocks 14.2 shocks 11.4 shocks	Threshold was higher in high-nic sm relative to all other conditions. Tolerance was higher for high-nic sm & ns relative to deprived sm. Tolerance not different between low-nic & all other conditions.
Pomerleau et al. (1984)	5 sm	CPT 4 °C	Nonsmokers Preferred-nic cigarette	8.2 shocks 45.0 s (45.3)	19.6 shocks 143.4 s (143.8)	Threshold nearly doubled for preferred-nic relative to zero-nic.
Fertig et al. (1986)	10 sm; 15 ex-sm	CPT 3 °C	Zero-nic cigarette Preferred-nic cigarette Nicotine snuff (ex-sm)	27.4 s (30.3) 24.2 s (8.6) 25.8 s (11.6)	113.0 s (121.5) 59.0 s (26.7) 56.9 s (23.5)	Tolerance higher for preferred-nic relative to zero-nic. Threshold & tolerance increased as a function of nicotine dose for smokers (preferred-nic) & ex-smokers (snuff). No differences between snuff, preferred-nic, or zero-nic & sham smoke.
Pauli et al. (1993)	9 sm	Thermal	Zero-nic cigarette Sham smoke cigarette Deprived 12 hr, then smoke Deprived < 30 min, then smoke	14.2 s (4.6) 11.7 s (3.4) ~+1.0 °C ~+0.2 °C	46.8 s (19.0) 35.0 s (16.6) Unspecified	Threshold (pre-smoking vs. post-smoking) increased for sm previously deprived for 12 hr but not for sm previously deprived for < 30 min.
Perkins et al. (1994)	10 sm; 10 ns	Thermal	Pre-post nic nasal spray	Unspecified	Unspecified	Threshold (pre-smoking vs. post-nic spray) higher for ns relative to sm.
Study 2 Study 3	12 sm; 12 ns 18 sm; 18 ns		Nic spray vs. Placebo spray Nic spray vs. Placebo spray			Threshold higher for nic spray among both sm and ns. Threshold higher for nic spray at 20ug/kg for sm & 10ug/kg for ns.
Lane et al. (1995)	18 sm	Thermal	Preferred-nic cigarette De-nic cigarette Overnight abstinence	+0.1 °C +0.2 °C -0.2 °C	+0.5 °C +0.0 °C -0.4 °C	Tolerance (pre-smoking vs. post-smoking) higher for preferred-nic relative to abstinence. Intermediate effects of de-nic on tolerance not different from the other 2 conditions. No threshold effects.
Jamner et al. (1998)	Male: (17 sm; 13 ns) Female: (21 sm; 23 ns)	Thermal	Male + Nicotine patch Male + Placebo patch Female + Nicotine patch Female + Placebo patch	7.1 mA (4.7) 5.9 mA (3.1) 2.9 mA (2.0) 2.9 mA (1.9)	8.9 mA (4.6) 7.6 mA (3.3) 4.3 mA (3.4) 4.2 mA (2.8)	Threshold and tolerance increased as a function of nicotine patch vs. placebo for male participants only.
Kanarek & Carrington (2004)	49 sm	CPT 2 °C	Smoke + Sucrose Smoke + Placebo No smoke + Sucrose No smoke + Placebo	20.3 s (2.7) 15.4 s (1.6) 14.5 s (1.2) 14.3 s (1.2)	46.1 s (4.3) 45.6 s (4.4) 36.1 s (3.3) 37.5 s (3.7)	Threshold and tolerance were increased when participants were permitted to smoke, relative to when they were not permitted to smoke. Sucrose consumption augmented the effects of smoking on pain threshold but not on pain tolerance.
Nastase et al. (2007)	23 sm	CPT 3 °C	Nic cigarette Nic cig + Coffee	+5.0 s (~) +10.0 s (~)	+12.0 s (~) +12.0 s (~)	Threshold (pre-smoking vs. post-smoking) increased with smoking. Coffee doubled the increase in pain threshold induced by smoking.

Note. The table was adapted from "Pain inhibition, nicotine, and gender," by L. D. Jamner, S. S. Girdler, D. Shapiro, & M. E. Jarvik, 1998, *Experimental and Clinical Psychopharmacology*, 6, p. 97. Copyright 1998 by American Psychological Association. The numbers in parentheses are standard deviations. CPT = cold-pressor test; thermal = thermal heat; mA = electrical current in milliamperes; (~) = approximate values; sm = smoker; ns = nonsmoker; ex-sm = ex-smoker; nic = nicotine; De-nic = de-nicotinized.

Table 2  
*Acute Effects of Nicotine and Tobacco on Pain Perception: Pain-Inhibitory Effects Not Observed*

Study	Participants	Pain	Conditions	Threshold	Tolerance	Primary findings
Waller et al. (1983)	33 sm	Electrical	Smoke Smoke + Beta Blocking Agent No smoke	Unspecified	Unspecified	No effect of smoking or beta blocker on pain threshold or tolerance.
Muser et al. (1984)	24 sm	Electrical	No smoke	Unspecified	Unspecified	No effect of smoking on pain threshold.
Shiffman & Jarvik (1984)	10 sm	Electrical	High-nic cigarette	18.0 shocks	Not analyzed	No effect of smoking on pain threshold.
Jarvik et al. (1989)	15 sm	CPT	Sham smoke Smoke Deprived	18.3 shocks Unspecified	40.1 s 36.3 s	No difference was found between the smoking and deprived conditions for either pain threshold or pain tolerance.
Sult & Moss (1986)	16 sm; 16 ns	Electrical and CPT	Sham smoke	Unspecified	Unspecified	No effect of smoking on threshold or tolerance for either CPT or electrical stimulation.
Knott (1990)	14 sm	Electrical	Moderate-nic cigarette Smoke Deprived	Unspecified	Unspecified	No effect of smoking on pain ratings. Smoking increased N1–P2 amplitudes to electrical stimulation.
Knott & De Lugt (1991)	24 sm	Electrical	Smoke No smoke 4 warming conditions	Unspecified	Unspecified	No effect of smoking on pain ratings. Increasing prepain warming stimulation resulted in highest pain ratings.
Unrod et al. (2004)	80 sm	CPT 3 °C	Smoke + Distraction	Unspecified	Unspecified	No effect of smoking on pain threshold or tolerance.
	40 male; 40 female		Smoke + No Distraction			Hypothesized Smoke $\times$ Distraction interaction was not significant.
			No Smoke + Distraction			Threshold and tolerance increased with distraction for men only.
			No Smoke + No Distraction			

*Note.* The table was adapted from "Pain inhibition, nicotine, and gender," by L. D. Jamner, S. S. Girdler, D. Shapiro, & M. E. Jarvik, 1998, *Experimental and Clinical Psychopharmacology*, 6, p. 97. Copyright 1998 by American Psychological Association. sm = smoker; ns = nonsmoker; N1–P2 = pain evoked middle latency EP amplitude; CPT = cold-pressor test.

1994; Yogeewari, Sriram, Ratan Bal, & Thirumurugan, 2006). Animal data indicate that the analgesic properties of epibatidine can be fully inhibited by the administration of centrally acting nicotinic antagonists (Rupniak et al., 1994) but not by opioid antagonists such as naloxone (Spande et al., 1992) or by antagonists incapable of crossing the blood-brain barrier (e.g., Damaj et al., 1998). For a more thorough discussion of how a wide distribution of nAChRs in the central and peripheral nervous systems may be implicated in the analgesic actions of nicotine, readers are directed to a recent review of the pathophysiology of pain and smoking (Shi et al., 2010).

**Endogenous opioids.** Whereas nicotine and other nAChR agonists (e.g., epibatidine) appear to have mostly central antinociceptive effects, these actions may also be mediated by the activation of endogenous opioid systems (e.g., Marubio et al., 1999; Wewers, Dhath, Snively, & Tejwani, 1999). Endogenous opioids are essential to descending pain inhibition, and the endogenous opioid system represents the best characterized pain modulatory system. Empirical evidence indicates that smoking stimulates the release of beta-endorphins (O. F. Pomerleau, 1992; O. F. Pomerleau, Fertig, Seyler, & Jaffe, 1983), and covariation between plasma concentrations of beta-endorphin and number of cigarettes smoked per day has been observed (del Arbol et al., 2000). Beta-endorphins are endogenous opioid polypeptide compounds that resemble opiates in their ability to produce analgesia. Often referred to as the body's natural painkiller, beta-endorphin is released by the pituitary gland into the blood and from hypothalamic neurons into the spinal cord and brain. In total, there are three families of endogenous opioid peptides (i.e., enkephalins, dynorphins, and endorphins), and their receptors include mu-, delta- and kappa-subtypes (Kieffer, 1999; Kiguchi et al., 2008). Each of these receptor subtypes have demonstrated effects of nicotine in spinally mediated antinociception (Campbell, Taylor, & Tizabi, 2007). Beta-endorphin has the highest affinity for the mu1-opioid receptor, slightly lower affinity for mu2- and delta-opioid receptors, and low affinity for kappa1-opioid receptors. Animal research has demonstrated that analgesic effects of nicotine are reduced in mu-opioid receptor gene knockout mice (Berrendero, Kieffer, & Maldonado, 2002) and mice lacking the preproenkephalin gene (Berrendero et al., 2005). A comprehensive analysis of nicotine-nAChR mediation via various components of the endogenous opioid system is beyond the scope of this review. However, several lines of research indicate that the antinociceptive effects of nicotine are likely mediated by both nicotinic and mu-opioid receptors (Galeote et al., 2006; Kwon et al., 2008; Simons et al., 2005). For more information on the role of dynorphins, methionine-enkephalins, and kappa peptides in nicotine-induced antinociception, see Galeote, Maldonado, and Berrendero (2008) and Kiguchi et al. (2008). For additional nAChR analgesic modulators, see a review by Jain (2004).

**Cardiovascular responses.** Another mechanism by which nicotine may modulate pain sensitivity is through its pressor actions on the cardiovascular system (Jamner et al., 1998). Reduced pain responding has been associated with greater cardiovascular reactivity (al'Absi, Buchanan, & Lovallo, 1996; al'Absi, Petersen, & Wittmers, 2000; Lovallo et al., 1996), and some studies provide direct evidence of reduced pain sensitivity among individuals with high blood pressure (Bruehl, Chung, Ward, Johnson, & McCubbin, 2002; Lewkowski, Ditto, Roussos, & Young, 2003; Lewkowski,

Young, Ghosh, & Ditto, 2008; K. W. Stewart & France, 1996). Moreover, nicotine administration has been shown to elevate blood pressure in smokers and nonsmokers (Argacha et al., 2008; Srivastava, Russell, Feyerabend, Masterson, & Rhodes, 1991; Tanus-Santos et al., 2001). With these associations in mind, researchers have suggested that nicotine-induced alterations in peripheral blood flow may have contributed to observed differences in pain sensitivity for male, relative to female, smokers (Jamner et al., 1998) and participants who smoked, relative to those who did not smoke (Kanarek & Carrington, 2004).

**Attentional narrowing.** An additional factor that has been shown to impact pain perception is attention, with numerous studies indicating that attentional focus is central to modulation of the pain experience (Arntz & de Jong, 1993; Eccleston & Crombez, 1999; McCaul, Monson, & Maki, 1992; Nouwen, Cloutier, Kappas, Warbrick, & Sheffield, 2006; Veldhuijzen, Kenemans, de Bruin, Olivier, & Volkerts, 2006). Kassel (1997) proposed that nicotine increases attentional resources and leads to attentional narrowing. Attentional narrowing is believed to restrict attention to a smaller number of the most salient environmental cues (Unrod et al., 2004). Thus, smoking may result in either greater awareness of painful stimuli when there is no alternative distractor to focus on or reduced awareness of pain when an additional salient distractor is present (e.g., engagement of a pain coping strategy).

**Additional factors.** Nicotine-mediated analgesia has also been hypothesized to involve the local release of norepinephrine, with activation of  $\alpha_2$ ,  $\alpha_4\beta_2$ , and  $\alpha_7$  adrenergic receptors (Benowitz, 2008b; Rowley & Flood, 2008; Rowley et al., 2008; Yogeewari et al., 2006), the serotonergic system (Damaj, Glennon, & Martin, 1994), hypothalamic-pituitary-adrenocortical activity (al'Absi, Wittmers, Hatsukami, & Westra, 2008; Girdler et al., 2005), and gamma-aminobutyric acid (GABA) receptor activity (Mui, Zbuzek, & Wu, 1997). Finally, nicotine has been shown to have anti-inflammatory actions that may result in diminished pain responding (Miao, Green, Benowitz, & Levine, 2004; Yoshikawa et al., 2006), with the nAChR receptor  $\alpha_7$  subunit identified as an essential regulator of inflammation (Wang et al., 2003).

**Summary and conclusions.** The animal literature appears to yield consistent and strong empirical support for direct pain-inhibitory effects of nicotine and tobacco smoke. Conversely, studies with humans have been less consistent. Possible explanations for why human investigations of smoking-related analgesia report mixed results include generally low statistical power, lack of uniformity in stimuli used to induce pain, interstudy variability in sample smoking-rates and nicotine dependence, and failure to assess potentially influential third variables (e.g., psychosocial and physiological factors). These same considerations may limit the applicability of meta-analytic techniques to the current corpus of human studies.

With regard to studies that did demonstrate nicotine-induced antinociception, several potential mechanisms have been suggested, including activation of nAChRs, pressor actions on the cardiovascular system, attentional narrowing, the release of norepinephrine and serotonin, hypothalamic-pituitary-adrenocortical activity, GABA receptor activity, and regulation of inflammatory responses. In addition, smoking has recently been shown to suppress pain-related evoked potentials (Miyazaki, Wang, Inui, Domino, & Kakigi, 2010). Finally, it is noteworthy that nicotine is currently being tested for its capacity to serve as a postoperative

analgesic (Benowitz, 2008b; Olson, Hong, Conell-Price, Cheng, & Flood, 2009).

Given the possibility of nicotine-related analgesic effects, one might hypothesize that smokers in pain would require less analgesic medication than nonsmokers. However, research indicates that this is not the case. In fact, smokers in pain (both postoperative and in the general population) appear to use substantially more analgesic medication than nonsmokers (Ackerman & Ahmad, 2007; Antonov & Isacson, 1996; Broekmans, Dobbels, Milisen, Morlion, & Vanderschueren, 2010; Creekmore, Lugo, & Weiland, 2004; Glasson, Sawyer, Lindley, & Ginsberg, 2002; John et al., 2006; Woodside, 2000). As can be inferred from the experimental literature reviewed herein, pain-inhibitory effects likely result from acute nicotine administration, whereas increased pain sensitivity may be function of chronic exposure to nicotine and tobacco smoke. Indeed, it has been suggested that chronic exposure to nicotine (or perhaps another component in tobacco smoke) may sensitize pain receptors, decrease pain tolerance, and increase pain awareness, thus resulting in a greater need for analgesic agents (Barton, Kofoed, & Doleys, 1989; Woodside, 2000). Another explanation for these apparently paradoxical findings is that smokers in postoperative settings may be experiencing symptoms of nicotine withdrawal. In fact, there is new evidence to suggest that withdrawal from tobacco smoking may lead to increased pain sensitivity via nAChR activity (Cosgrove et al., 2010).

### Effects of Pain on Smoking

#### Pain as a Motivator of Smoking

In contrast to evidence that smoking may have analgesic effects or serve as a risk factor for developing or exacerbating some types of chronic pain, there is reason to believe that some smokers may be motivated to use tobacco in response to pain. Indeed, researchers have suggested that the avoidance or relief of pain, or both, might be a potent reinforcer in the maintenance of tobacco smoking and nicotine dependence (Fertig et al., 1986; Fishbain et al., 2007; Jarvik et al., 1989; O. F. Pomerleau, 1986; Silverstein, 1982; Zvolensky et al., 2009). In the following section, we first review evidence of covariation between pain intensity and smoking behavior. We then draw from the literature on stress, negative affect, and smoking to better focus our conceptualization of pain as a motivator of smoking. Next, we review initial cross-sectional and experimental evidence that pain may serve to increase self-reported desire to smoke and subsequent smoking behavior. Finally, we propose several potential mechanisms of action.

**Covariation between pain intensity and smoking behavior.** Numerous studies provide evidence of covariation between pain intensity and smoking behavior. An early national survey of pain in the United States revealed a positive correlation between pain and smoking, such that as self-reported pain severity increased, there was a tendency for respondents to smoke more and exercise less (Sternbach, 1986). More recently, dose-response relations between pain intensity/disease severity and the number of cigarettes smoked per day have been observed among smokers in the general population who endorsed significant past-week pain (Hahn, Rayens, Kirsh, & Passik, 2006) and persons with temporomandibular disorder (Melis et al., 2010), orofacial pain (Riley et al., 2004), fibromyalgia (Yunus et al., 2002), RA (Saag et al., 1997), and

chronic back pain (Andersson, Ejlerthsson, & Leden, 1998; Deyo & Bass, 1989; Kaila-Kangas, Leino-Arjas, Riihimaki, Luukkonen, & Kirjonen, 2003; Oleske et al., 2004; Scott, Goldberg, Mayo, Stock, & Poitras, 1999). Current smoking has also been positively associated with ratings of pain severity among general chronic pain patients (Davidson, Davidson, Tripp, & Borschch, 2005; Fishbain et al., 2007; Weingarten et al., 2008), persons with painful temporomandibular joint disorders (Weingarten, Iverson, et al., 2009), patients evaluated at a specialized fibromyalgia treatment program (Weingarten, Podduturu, et al., 2009), persons with cancer (Daniel et al., 2009; Ditre et al., 2011; Logan et al., 2010), and persons with herpes zoster and postherpetic neuralgia (Parruti et al., 2010). Finally, there is some evidence of a correlation between pain severity and level of nicotine dependence (Weingarten et al., 2008). It is important to note, however, that the observed covariance between pain and smoking may reflect either the use of tobacco to cope with pain, the aforementioned findings that smoking may be a risk factor for the development or exacerbation of painful conditions, or both. That is, the direction of causality is unclear.

**Stress and negative affect as motivators of smoking.** Pain is inherently unpleasant (Fillingim, 2005), and pain affect has been characterized in terms of affective distress, emotional arousal, and disruption produced by the pain experience (Jensen & Karoly, 2001; Melzack, 1975). It therefore seems prudent to extrapolate from the extensive literature on interrelations between nicotine, tobacco, and negative affect when considering how pain may serve to motivate smoking behavior. Within this broad framework, it is important to draw a distinction between data that support the role of affective distress as an agent in the maintenance of smoking and less conclusive data regarding the purported mood-modulating effects of nicotine and tobacco smoking. Indeed, stress and negative affect may promote self-administration of nicotine, even in the absence of true emotion-modulating effects (Kassel, Stroud, & Paronis, 2003). In a seminal review of smoking, stress, and negative affect, Kassel et al. (2003) concluded that tobacco-dependent smokers consistently endorse increased smoking in response to self-reported stress and negative affect (e.g., Aronson, Almeida, Stawski, Klein, & Kozlowski, 2008; Creson, Schmitz, & Arnoultovic, 1996; Hellerstedt & Jeffery, 1997; Steptoe, Wardle, Pollard, Canaan, & Davies, 1996) and that various manifestations of negative affect often precede smoking lapses and relapse to regular smoking among those attempting to quit (e.g., Brandon, Tiffany, Obremski, & Baker, 1990; Cummings, Jaen, & Giovino, 1985; Shiffman, 1982). The results of data collected in naturalistic settings corroborate these findings, with perceived stress shown to trigger smoking urges/cigarette consumption (Todd, 2004) and smoking lapses among recent quitters (Shiffman, Paty, Gnys, Kassel, & Hickcox, 1996).

These observations are further supported by experimental studies with humans and animals. For example, the results of several studies with humans provide evidence of a causal relation between laboratory-induced stress and increased motivation to smoke, as indexed by the self-reported urge to smoke, increased cigarette consumption, and more intense smoking behavior (e.g., Kotlyar et al., 2011; Perkins & Grobe, 1992; C. S. Pomerleau & Pomerleau, 1987; Rose, Ananda, & Jarvik, 1983). Similar findings have been obtained using animal models, in which experimental stress-induction (e.g., foot shock) has resulted in the self-administration



of several substances (e.g., cocaine, heroin), including nicotine (Bilkei-Gorzo et al., 2008; Buczek, Le, Wang, Stewart, & Shaham, 1999; Yamada & Bruijnzeel, 2011). Given the consistent empirical support for stress and negative affect as a motivator of smoking, it seems intuitive to suggest that pain may promote smoking and to hypothesize that pain may predict relapse among persons with chronically painful conditions.

#### **Pain as a motivator of smoking.**

**Cross-sectional evidence.** An influential cross-sectional investigation into the relation between pain and smoking among treatment-seeking chronic pain patients revealed that 57% of 134 smokers reported an increased desire to smoke tobacco when experiencing pain (Jamison et al., 1991). Furthermore, those who endorsed smoking in response to pain demonstrated higher self- and physician-rated emotionality, increased dissatisfaction with their social lives, reduced interest in social and recreational activities, increased reliance on opioid medications, and more frequent rates of bed confinement. Consistent with evidence of covariation between pain and smoking, those patients who endorsed a pain-induced craving to smoke also described their chronic pain as more constant and used a greater number of pain descriptors when describing their condition. Jamison et al. (1991) concluded that pain patients who demonstrated greater emotionality and physical inactivity were at increased risk for smoking when experiencing pain.

A more recent qualitative study revealed that smokers participating in a multidisciplinary pain treatment program consistently endorsed tobacco smoking as a means of coping with their pain (Hooten, Vickers, et al., 2011). They also reported that smoking served to distract them from pain and modulate emotional distress, that the experience of pain tended to increase desire to smoke, and that their motivation to smoke was influenced by their use of opioid pain medications.

**Prospective evidence.** We are aware of only one study that examined prospective, temporal relations between pain onset and subsequent smoking status (Waldie et al., 2008). Within a longitudinal cohort design, smoking behavior and headache activity of 979 participants were assessed at several time points, including childhood (ages 11–13 years), midadolescence (age 15 years), and adulthood (age 26 years). After controlling for gender and parental socioeconomic status (i.e., occupational, educational, income), results indicated that adolescents who reported frequent headaches (relative to those who did not) were more than twice as likely to endorse regular smoking in adulthood (OR = 2.20, 95% CI [1.3, 3.7]). Adult smokers were also less likely to have quit smoking if they reported frequent headaches during midadolescence, with more intense (e.g., migraine) headache sufferers significantly more likely to have tried unsuccessfully to quit smoking than those with less severe (e.g., tension-type) headache presentations.

**Experimental evidence.** The extant experimental literature on pain and smoking has focused almost exclusively on whether nicotine or tobacco may influence pain reporting. In contrast, Ditre and Brandon (2008) conducted the first experimental investigation into the effect of pain on motivation to smoke tobacco. Specifically, they hypothesized that laboratory-induced cold-pressor pain would elicit greater urges to smoke and increases in immediate smoking behavior. In this crossed-factorial between-subjects design, 132 nicotine-dependent smokers were randomly assigned to either pain (cold pressor maintained between 0–1 °C) or no-pain

(cold pressor maintained at room temperature) conditions. Following the pain manipulation, all participants completed measures of mood and desire to smoke and were given the opportunity to smoke one of their own cigarettes. As hypothesized, participants who underwent pain induction reported significantly greater smoking urges and demonstrated shorter latency to smoke (i.e., lit their cigarette faster) than participants in the no-pain condition. Observed effect sizes for pain-induced urge ( $f = .39$ ) and decreased latency to smoke ( $f = .20$ ) were classified as large and medium, respectively. Results also indicated that the causal relation between pain and increased craving was only partially mediated by pain-induced negative affect, suggesting that modulation of mood was not solely responsible for the observed effects. This study provided the first experimental evidence that situational pain could be a potent motivator of smoking.

Ditre et al. (Ditre, Heckman, Butts, & Brandon, 2010) conducted a follow-up study to further establish the role of pain as a motivator of smoking and to explicate mechanisms underlying the observed causal relation between experimentally induced pain and increased desire to smoke. Specifically, these authors hypothesized that manipulations designed to challenge smoking-related outcome expectancies for pain coping (expectancy challenge) and implement an effective pain coping strategy (coping enhancement) would each reduce post-pain induction motivation to smoke, relative to control conditions. Nicotine-dependent smokers ( $N = 132$ ) were randomly assigned to one of four conditions in this  $2 \times 2$  crossed-factorial between-subjects design. As hypothesized, tobacco smokers randomized to either expectancy challenge or coping conditions reported reduced smoking urges and demonstrated longer latencies to smoke following experimental pain induction. Expectancy challenge smokers also took fewer puffs and spent less time smoking than did controls. Observed effect sizes ranged from large ( $f = .39$ ) to medium ( $f = .24$ ) for expectancy and coping manipulations of pain-induced urge to smoke, respectively. An interaction effect revealed that although each manipulation was sufficient to reduce smoking urges, the combination was found to be neither additive nor synergistic. Ditre et al. (2010) concluded that the causal pathway underlying experimental pain as a motivator of smoking could be disrupted by invoking social cognitive theory-based constructs known to influence smoking behavior and pain reactivity. It was further suggested that these constructs might warrant consideration in the development of targeted interventions for persons with comorbid pain and substance use disorders.

**Possible mechanisms.** Individuals with chronic pain have offered a number of anecdotal reasons for their tendency to report increased smoking in response to pain (Hooten, Vickers, et al., 2011; Jamison et al., 1991). Some of these included the expectancy that smoking assists in coping with pain (e.g., via distraction), relief from pain-related boredom, anxiety, depression, anger, and frustration (i.e., negative reinforcement), and enjoyment derived from smoking (i.e., positive reinforcement). In addition to these considerations, we also explore potential neurobiological mechanisms of action.

**Smoking-related outcome expectancies.** An outcome expectancy is an individual's estimate that a particular behavior will lead to certain positive outcomes (Bandura, 1977). Expectancies may also be conceptualized as dynamic, memory-based information templates that become part of anticipatory, automatic behavioral sequences leading to the use of substances (Goldman, 1999, 2002).

Within this contemporary perspective, expectancies serve as an example of hot information processing linked inextricably to affective and motivational processes (Brandon, Herzog, Irvin, & Gwaltney, 2004). With regard to smoking, nicotine-dependent smokers tend to hold more stable (trait-like) positive expectancies about the consequences of tobacco smoking than do lighter smokers or nonsmokers (Brandon, Juliano, & Copeland, 1999). Smokers also appear to hold proximal, situation-specific smoking-related outcome expectancies (e.g., that smoking can alleviate negative mood states) that are capable of motivating smoking behavior (Brandon et al., 1999; Copeland & Brandon, 2000; Gonzalez, Hogan, McLeish, & Zvolensky, 2010; Rotter, 1978). Thus, it stands to reason that sensory and affective components of the pain response would interact with pain-related cognitive appraisals to activate positive smoking-related outcome expectancies for mood modulation and/or pain reduction, leading to increased craving and cigarette consumption. Indeed, as noted, there is recent evidence that a manipulation designed to reduce smoking-related outcome expectancies for pain-coping resulted in decreased motivation to smoke following experimental pain induction (Ditre et al., 2010). It is also important to note that expectancies do not have to be accurate in order for them to motivate behavior (Brandon et al., 2004). That is, a smoker's expectancies regarding tobacco's ability to distract one from pain or mitigate negative affect may motivate smoking behavior regardless of whether these expectancies actually hold true for the given smoker. This matter is further complicated in that expectancies themselves may be capable of producing some expected responses (i.e., the placebo effect; Juliano & Brandon, 2002; Kirsch, 1985).

**Negative reinforcement.** Negative reinforcement models of addiction motivation assert that self-administration of a substance is contingent on the extent to which it serves to terminate or mitigate an aversive event (e.g., Baker, Piper, McCarthy, Majeskie, & Fiore, 2004; Wikler, 1948). Leading models of negative reinforcement from smoking include withdrawal-based, classical conditioning, self-medication, and opponent-process (see review by Eissenberg, 2004). With regard to explaining why pain may come to motivate smoking, we focus on self-medication models and key concepts associated with both withdrawal-based and classical conditioning models of negative reinforcement.

Self-medication and stress-coping models are relevant to conceptualizing pain as a motivator of smoking because they emphasize that substance use is motivated and reinforced by the desire to reduce or cope with stress and negative affect (e.g., Khantzian, 1997; Wills & Shiffman, 1985). Indeed, there is accumulating empirical support for the role of self-medication in the maintenance of tobacco smoking (Dierker, Avenevoli, Merikangas, Flaherty, & Stolar, 2001; Farrell et al., 2001; Glassman et al., 1990; S. H. Stewart, Karp, Pihl, & Peterson, 1997), and the multitude of stressors associated with chronically painful conditions provide a powerful context for examining these assumptions. Furthermore, this process of using substances to cope is believed to hinder the development and engagement of more adaptive coping strategies leading to greater dependence (Cooper, Russell, & George, 1988).

Withdrawal-based models emphasize drug use that is reinforced by escape or avoidance of an aversive withdrawal state. The smoking withdrawal syndrome typically consists of craving to smoke, irritability, anxiety, depression/dysphoria, difficulty concentrating, restlessness, sleep disturbance, and decreased heart rate

(e.g., Hendricks, Ditre, Drobles, & Brandon, 2006; Hughes, 1991). Classical conditioning models suggest that during self-administration of substances such as nicotine, previously neutral stimuli become associated with the unconditioned pharmacological effects of the drug. The authors of a recently reformulated model of negative reinforcement from smoking proposed that as individuals learn to self-administer drugs in response to aversive withdrawal effects, they might generalize this learning to other nonpharmacologic sources of negative affect, resulting in either being sufficient to motivate drug-seeking behavior (Baker, Piper, et al., 2004). Baker et al. (2004) further proposed that through repeated cycles of drug use and withdrawal, addicted individuals might learn to detect interoceptive cues associated with negative affect, both consciously and preconsciously. Within the framework of the current review, we suggest that as pain becomes increasingly linked with the acquisition and delivery of nicotine to suppress withdrawal and other forms of negative affect, it may gain salience as an interoceptive cue for smoking. Interoceptive conditioned stimuli (i.e., negative mood states) have been shown to result in conditioned responses among tobacco smokers (Brandon, Wetter, & Baker, 1996). Such findings are clinically relevant because affectively valenced cues have been shown to increase the self-reported craving to smoke (Litvin & Brandon, 2010; Maude-Griffin & Tiffany, 1996; Tiffany, 1990) and because conditioned responses likely contribute to drug use maintenance (Rohsenow, Niaura, Childress, Abrams, & Monti, 1990) and relapse (Brandon, Vidrine, & Litvin, 2007). Thus, we suggest that over time, chronic pain may serve to maintain tobacco dependence and present a barrier to smoking cessation.

**Positive reinforcement.** Smoking may enhance positive affect, increase energy/arousal, and improve cognitive performance. Laboratory self-administration models have shown nicotine to be positively reinforcing among both human participants and animal subjects (Benowitz, 2008a). A meta-analytic review of 15 placebo-controlled human studies showed nicotine administered intravenously or via nasal spray to be associated with greater ratings of drug-related liking, high, and vigor (Kalman & Smith, 2005). A more recent meta-analysis of 41 double-blind, placebo-controlled human studies concluded that smoking significantly enhanced motor abilities, attention, and memory (Heishman, Kleykamp, & Singleton, 2010). Tobacco-dependent smokers also tend to endorse smoking-related outcome expectancies for affect enhancement and sensory enjoyment (Baker, Brandon, & Chassin, 2004; Brandon & Baker, 1991; Copeland, Brandon, & Quinn, 1995), and desire for positive reinforcement has been shown to increase urge/intention to smoke (Cox, Tiffany, & Christen, 2001; Tiffany & Drobles, 1991).

There is reason to believe that desire for positive reinforcement may motivate smoking among individuals with chronic pain. Chronic pain has been associated with reduced participation in social or recreational activities (Closs, 2009), increased absence from work and unemployment (Braden et al., 2008), lower perceived social support (Carr & Moffett, 2005), and loneliness (Løylund, Miaskowski, Paul, Dahl, & Rustoen, 2010). According to behavioral activation theory, humans are sensitive to the availability of positive reinforcers, and a reduction in positive reinforcement can lead to depression and the engagement of potentially maladaptive coping responses (Dimidjian, Martell, Addis, Herman-Dunn, & Barlow, 2008). Jamison et al. (1991) suggested

that individuals in pain may turn to activities such as eating and smoking to maintain stable rates of positive reinforcement when other environmental reinforcers have been removed. Importantly, there is experimental evidence to suggest that the hedonic effects of smoking may be greatest among smokers with low baseline levels of positive affect (J. W. Cook, Spring, & McChargue, 2007). In addition, positive affect has been found to restore depleted self-control resources (Tice, Baumeister, Shmueli, & Muraven, 2007), and there is recent evidence that smoking may also restore self-control via enhancement of positive affect (Heckman, Ditte, & Brandon, 2011). Given that coping with pain likely taxes self-control, smoking may be reinforced in chronic pain patients by the restoration of self-control resources via positive affect. Finally, delay discounting theory posits that the immediacy of a potential reinforcer is an important component of substance-use motivation (Glautier, 2004), and tobacco smoking may be the most available and immediate source of positive reinforcement among smokers with chronic pain.

**Neurobiological considerations.** As discussed above, withdrawal-based and classical conditioning models of negative reinforcement suggest that over time, pain may increase reactivity to smoking-related cues and that pain itself may come to serve an interoceptive cue for smoking. Research on the neurobiological basis of drug cue reactivity suggests that neural circuits involved in emotion and reward learning may play a central role in these processes (Phillips, Stuber, Heien, Wightman, & Carelli, 2003; Volkow, Fowler, & Wang, 2004). Indeed, there is evidence that the mesolimbic dopamine reward system may mediate the acquisition of conditioned associations between nicotine (unconditioned stimulus) and smoking (conditioned stimulus) cues (Balfour, Wright, Benwell, & Birrell, 2000; Di Chiara, Loddo, & Tanda, 1999). When nicotine stimulates dopaminergic neurons in the ventral tegmental area (VTA), dopamine floods the nucleus accumbens shell, and this reward signal increases the incentive salience of cues associated with nicotine self-administration. Through this mechanism, previously neutral and even aversive painful stimuli associated with tobacco smoking can become conditioned cues that release dopamine and increase the desire to smoke (Phillips et al., 2003).

Increased activity in the reward system is accompanied by compensatory increased activity in the neural stress system, including the amygdala, bed nucleus of stria terminalis (BNST), and hypothalamus (Everitt, Dickinson, & Robbins, 2001; Gerrits, Lesscher, & van Ree, 2003; Koob & Le Moal, 2001). Consequently, pain-induced stress may also increase cue reactivity by enhancing mesolimbic dopamine transmission. Support for this hypothesis can be derived from animal studies, which have demonstrated an association between stress-induced dopamine release and subsequent drug seeking (Shaham & Stewart, 1995). Moreover, the results of human studies have indicated that stress-induced drug craving was predicted by dopamine gene polymorphisms (Erblich, Lerman, Self, Diaz, & Bovbjerg, 2004), suggesting that genetic differences in dopamine release might influence the magnitude of stress-induced craving and drug seeking during the experience of stress and pain. Thus, while smoking cues and pain-induced stress may act on slightly different but overlapping neural substrates, both mechanisms may act synergistically to motivate smoking.

Pain-related stress may also trigger relapse following periods of abstinence from smoking. Support for this view can be derived

from animal models of stress-induced relapse, which have demonstrated that exposure to physically painful stressors can reinstate extinguished nicotine, heroin, cocaine, and alcohol drug-seeking behavior in rats (Buczek et al., 1999; Erb, Salmaso, Rodaros, & Stewart, 2001; Liu & Weiss, 2002; Shaham & Stewart, 1995; Zislis, Desai, Prado, Shah, & Bruijnzeel, 2007). In these studies, rats were trained to self-administer nicotine, and drug seeking was extinguished by substituting saline for nicotine. Following extinction, exposure to painful foot shock reinstated the drug-seeking behavior (Bruijnzeel, Prado, & Isaac, 2009; Zislis et al., 2007). Moreover, whereas painful shocks were shown to reinstate nonreinforced responding for addictive substances, they did not reinstate responding for natural reinforcers, such as sucrose and food pellets (Ahmed & Koob, 1997; Buczek et al., 1999; Lê et al., 1998; Mantsch & Goeders, 1999; Zislis et al., 2007).

Studies investigating the neural mechanisms underlying stress-induced relapse have focused on the role of corticotropin-releasing factor (CRF) and noradrenergic transmission in the BNST and the central nucleus of the amygdala (Bossert, Ghitza, Lu, Epstein, & Shaham, 2005; Shaham, Shalev, Lu, De Wit, & Stewart, 2003; Shalev, Erb, & Shaham, 2010; Zislis et al., 2007). CRF binds to receptors in the paraventricular hypothalamic nucleus to activate the hypothalamic-pituitary-adrenal (HPA) axis, leading to the release of cortisol (or corticosterone in rats) by the adrenal cortex (Dallman, Akana, Strack, Hanson, & Sebastian, 1995). CRF receptors located in both hypothalamic and extrahypothalamic brain sites have been shown to play an important role in mediating stress responses (De Souza, Moore, Raha, & Reed, 1995; Dunn & Berridge, 1990; Van Pett et al., 2000). CRF also contributes to the aversive emotional states associated with withdrawal from nicotine and other drugs and leads to increased drug consumption following abstinence (Bruijnzeel et al., 2009; Heilig & Koob, 2007; Koob, 2008; Sarnyai, Shaham, & Heinrichs, 2001). Moreover, the effect of painful stressors, such as foot shock, on reinstatement of nicotine self-administration appears to be mediated by increased activity of the CRF system (Bruijnzeel et al., 2009; Zislis et al., 2007). Indeed, administration of CRF1 receptor antagonists have been shown to prevent the deficit in brain reward function observed during nicotine withdrawal, as well as stress-induced reinstatement of nicotine-seeking behavior. The role of CRF in stress-induced relapse appears to be similar across different stressors and substances (Shalev et al., 2010).

Noradrenergic transmission in the central nucleus of amygdala (CeA) has also been shown to influence stress-induced reinstatement of nicotine seeking behavior. Both intraventricular (Zislis et al., 2007) and intra-CeA infusion (Bruijnzeel et al., 2009) of  $\alpha$ 2-adrenergic receptor agonists (clonidine or dexmedetomidine) have been demonstrated to attenuate stress-induced reinstatement of nicotine seeking. These findings suggest that CRF1 and  $\alpha$ 2-adrenergic receptor antagonists may be used to preempt pain-induced relapse following smoking cessation.

## Summary and Conclusions

There is burgeoning cross-sectional, prospective, and experimental evidence that tobacco smokers may experience greater motivation to smoke in response to pain. Although there appears to be significant covariation between pain intensity and smoking behavior among individuals with chronic pain and in the general

population, causal evidence for pain as a motivator of smoking is currently limited. Additional research conducted in naturalistic settings (perhaps using ecological momentary assessment) is necessary to establish the temporal precedence of pain and increased desire to smoke/smoking behavior (e.g., Stone & Shiffman, 1994).

The notion that smokers may believe that tobacco smoking will help them manage aversive sensory, affective, and cognitive states descriptive of the pain experience has great intuitive appeal and is supported by the empirical literature on associations between smoking, stress, and negative affect (Kassel et al., 2003). Furthermore, individuals with chronic pain have directly endorsed increased smoking in response to pain, despite acknowledging that smoking did little to reduce their pain (Jamison et al., 1991). Indeed, beliefs regarding the mood-modulating effects of smoking do not have to be true in order for them to motivate smoking behavior (Brandon et al., 2004). Finally, we suggested that purported pain-induced motivation to smoke may be partially explained by smoking-related outcome expectancies, negative reinforcement (e.g., self-medication and withdrawal-based learning), desire for positive reinforcement, and several underlying neurobiological processes.

Researchers have long proposed that pain may be a powerful reinforcer in the maintenance of tobacco smoking and nicotine dependence. More recently, it has been suggested that in the absence of more adaptive coping responses, persons with chronic

pain may learn to rely on smoking to manage noxious internal states (Zvolensky et al., 2010). Additional prospective evidence that pain motivates smoking, including the identification of relevant mediating and moderating factors, may contribute to the development of targeted smoking prevention, cessation, and relapse prevention interventions for individuals with chronic pain.

### An Integrative Reciprocal Model of Pain and Smoking

There is evidence that tobacco smoking may be a risk factor for the development and exacerbation of pain (*effects of smoking on pain*) and that pain may serve to motivate smoking (*effects of pain on smoking*). By integrating these two directions of empirical inquiry, we hypothesized a reciprocal relation between pain and smoking that acts as a positive feedback loop, with the end result being increased pain and the maintenance of tobacco dependence (Ditre & Brandon, 2008). The currently proposed reciprocal model of pain and smoking (see Figure 2) was adapted from an established four-stage model of pain processing (Price, 1999; Wade, Dougherty, Archer, & Price, 1996; Wade et al., 1992) and was updated to better integrate proposed mechanisms of action as extrapolated from a variety of biopsychosocial perspectives.

The four-stage model of pain processing proposed by Wade et al. (1996, 1992) and Price (1999) consists of (a) an initial sensory-discrimination stage, which we labeled *pain experience* to reflect

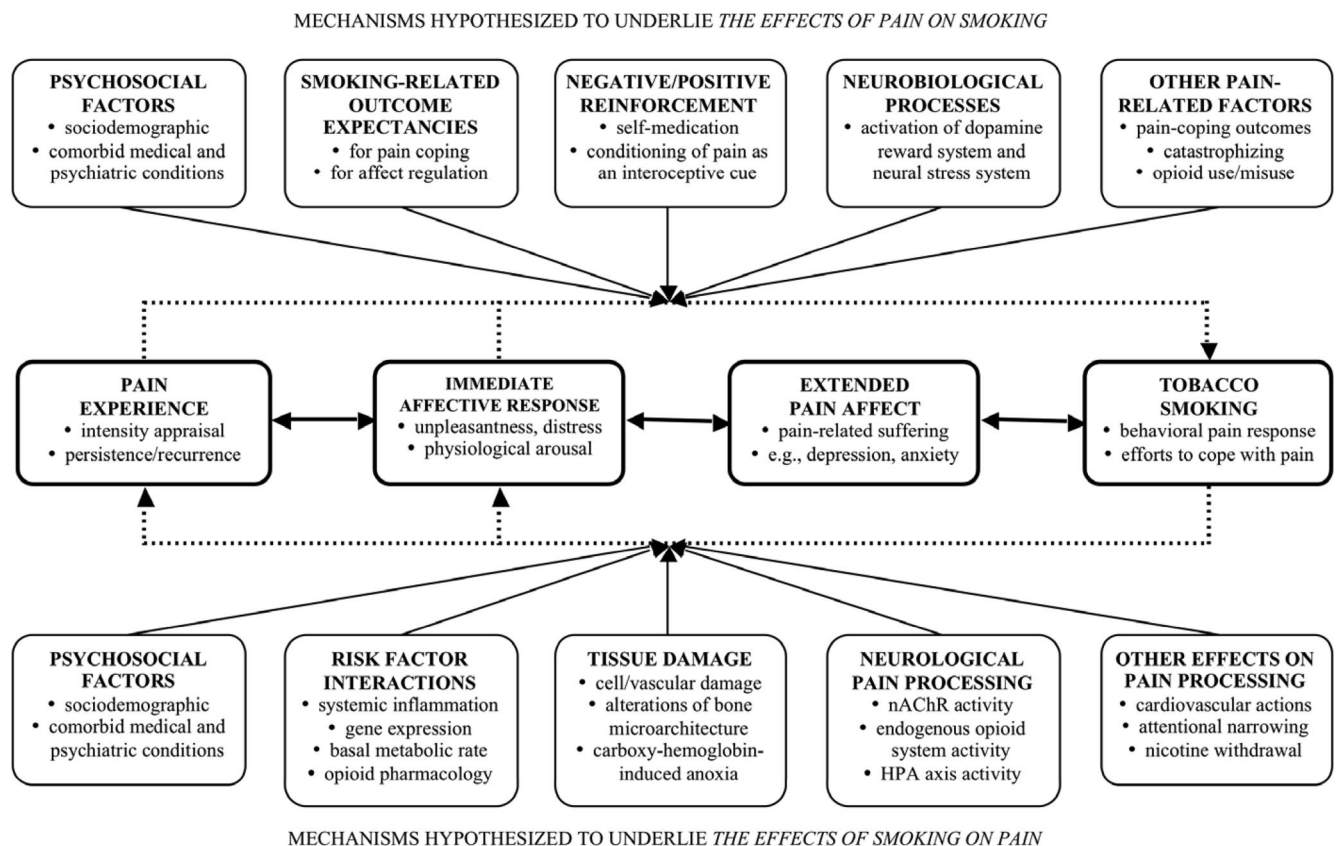


Figure 2. An integrative reciprocal model of pain and smoking. The lines were dashed to illustrate the modest causal support yielded by the extant literature on pain and smoking. nAChR = nicotinic acetylcholine receptors; HPA = hypothalamic-pituitary-adrenal.



appraisals of immediate pain intensity and recurrent/persistent pain; (b) a second stage, *immediate affective response*, representative of pain unpleasantness, distress, and physiological arousal; (c) an *extended pain affect* stage that reflects cognitive processes related to real or imagined long-term implications of pain as manifested by suffering, which may include depression, frustration, anxiety and anger; and (d) an overt behavioral stage, which for our purposes we labeled *tobacco smoking*, that subsumes any behaviors employed to manage or reduce pain (Riley & Price, 2004). The bidirectional arrows acknowledge that although the stages can be sequential, reciprocal influences can occur at any stage of pain processing. According to Riley and Price (2004), the four-stage model is consistent with clinical and experimental studies of pain modulation and neural mechanisms (e.g., serial and parallel processing) associated with sensory and affective dimensions of the pain experience.

The dashed lines surrounding the four-stage model were incorporated to better delineate purported *effects of smoking on pain* from purported *effects of pain on smoking*. The lines were dashed to illustrate the modest causal support yielded by the extant literature on pain and smoking. This presentation also allowed for clear demarcation between hypothesized mechanisms of action. As seen in Figure 2, mechanisms hypothesized to underlie the *effects of pain on smoking* include (a) psychosocial factors; (b) smoking-related outcome expectancies for pain coping and affect regulation; (c) negative reinforcement, including pain as a conditioned interoceptive cue for smoking to regulate pain-induced negative affect; (d) smoking as a form of positive reinforcement; (e) activation of the mesolimbic dopamine reward system and the neural stress system; and (f) other pain-related factors, such as whether an adaptive pain-coping strategy was employed/successful, tendency to catastrophize or employ maladaptive forms of coping, and use or misuse of analgesic medications. Mechanisms hypothesized to underlie the *effects of smoking on pain* include (a) psychosocial factors; (b) whether smoking may interact with other risk factors in the development or exacerbation of pain; (c) pain associated with or complicated by a broad spectrum of tissue damage resulting from regular smoking; (d) smoking-induced modulation of neurological processes resulting in pain-related sensitization, desensitization, and neuroplasticity; and (e) altered pain processing resulting from smoking-related cardiovascular pressor actions, attentional and cognitive narrowing, and nicotine withdrawal effects. Of course, the positive feedback loop is prevented from infinite amplification by self-limiting factors such as physiological limits on pain (e.g., type of pain, underlying pathophysiology, pain perception); physiological limits on smoking behavior or reinforcement from smoking (e.g., death, disability, unconsciousness, limits on nicotine metabolism, neuroadaptation from chronic nicotine administration); and social/environmental constraints on smoking (e.g., environmental smoking policies, cigarette taxation).

### Future Research and Clinical Implications

We conclude our review with an abbreviated set of recommendations for advancing research and practice in the area of pain and smoking comorbidity. The suggested research directions broadly address the construct validity of the proposed reciprocal relation between pain and smoking and allow for further refinement of the

integrative model, with the ultimate goal of improving clinical services for persons suffering from both conditions.

### Evaluation of Factors Common to Pain and Smoking

As referenced throughout the current review, there are numerous biopsychosocial factors that may contribute to the observed interrelationships between pain and tobacco smoking (i.e., confounding or third variables). Future research should employ a deliberate, epidemiologic approach to the investigation of factors common to both chronic pain and tobacco dependence. Specifically, we propose population-based studies of current, former, and never smokers with and without chronic pain, so as to produce base rate-corrected comorbidity estimates, while identifying causal or moderating links between the conditions.

### Prospective Studies of Smoking and the Development of Chronic Pain

Although there is substantial evidence of covariation between smoking and the development of chronic pain, direct causal evidence is limited. Additional prospective studies are needed to clarify the temporal precedence of smoking and chronic pain onset. Future studies would also benefit from an examination of trajectories of pain and smoking in greater resolution, while simultaneously accounting for the influence of potential third variables. Indeed, such relations may vary as function of the chronic pain condition itself (e.g., etiology, severity, operational definition, duration, and whether there are known pathological causes), smoking status (i.e., current, former, never), and a multitude of continuous smoking-related variables (e.g., age at initiation, average number of cigarettes smoked per day, duration of regular smoking, level of nicotine dependence, amount of time since quitting, current motivation to quit, difficulty quitting). For example, whereas a never smoker is commonly defined as someone who has smoked fewer than 100 cigarettes per lifetime (CDC, 2010b), there can be a great deal of variability in the smoking histories of current and former smokers.

### Experimental Analysis of Pain as a Motivator of Smoking

Experimental models for testing pain as a motivator of smoking offer a number of advantages, including standardization of painful stimuli; reliable and valid measurement of sensory, cognitive, and affective aspects of the pain experience; systematic assessment and manipulation of hypothesized mediators/moderators; and the ability to demonstrate casual relations. Laboratory-based paradigms have the potential to uncover important theory-based mechanisms that may inform the development of targeted interventions for persons with comorbid pain and addiction disorders. Future research into the effects of pain as a motivator of smoking should incorporate testing of pain modalities that are better analogues to chronic pain, across different subpopulations of smokers, including those with preexisting chronic pain conditions. It may also be useful to examine what the potential dose-response relations between pain intensity and motivation to smoke are, how the effect of pain-induced motivation to smoke may be amplified in the context of early withdrawal, and what is the extent to which experimental pain responding may predict smoking-related treat-

ment outcomes. Indeed, there is new evidence that experimental pain sensitivity measured prior to quitting predicted relapse to smoking (Nakajima & Al'absi, 2011). Finally, the motivational properties of pain should be tested at within- and between-subjects levels of analysis (e.g., Kassel et al., 2003).

### Naturalistic Assessment of Covariance Between Pain and Smoking

Increased understanding of dynamic, transitory interactions between pain and smoking could have important implications for explicating observed interrelations and developing targeted interventions. Such temporal resolution would ideally be examined in real-time, naturalistic settings, perhaps using ecological momentary assessment (e.g., Stone & Shiffman, 1994). Recent technological advances provide a host of options for multilevel daily assessment, including personal digital assistants, cell phones and smart phones, mobile broadband Internet devices, and ambulatory physiological monitoring systems. Less dynamic options include the use of daily diaries and brief telephone surveys. Most recently, for example, short message service (SMS) text was demonstrated to be a user-friendly and low-cost option for ecologically measuring real-time health behaviors (Berkman, Dickenson, Falk, & Lieberman, 2011).

### Smoking Cessation and Treatment for Chronic Pain

To our knowledge, there have been no published studies that examined how the engagement or completion of treatment for chronic pain may influence smoking-related factors such as the urge to smoke, smoking behavior, motivation to quit, or cessation-related outcomes. There have also been no studies that examined how quitting smoking or undergoing a quit attempt may influence sensory, affective, or cognitive manifestations of pain. Future research with respect to each of these treatment-related outcomes is sorely needed. Indeed, there are likely complex interactions between tobacco smoking, chronic pain, mood factors, and substance use (e.g., alcohol, opioid medications, and other licit/illicit drugs) that are highly relevant to the treatment of smoking and pain (e.g., Fishbain et al., 2007, 2009; Hooten, Shi, et al., 2011). To date, only two studies have examined the effect of smoking status on multidisciplinary pain treatment outcomes, with one reporting that some treatment responses were diminished among smokers (Fishbain et al., 2008) and the other reporting that treatment effects were either similar or enhanced among smokers (Hooten et al., 2009). There have also been only two studies that assessed readiness to quit smoking among individuals in pain (Hahn et al., 2006; Hooten et al., 2009), with both noting that pain does not appear to adversely impact interest in quitting. Finally, there have been no randomized controlled trials designed to evaluate the potential benefits of incorporating either pain- or smoking-relevant treatment components into existing interventions for tobacco dependence or chronic pain.

### Integrating Treatments for Chronic Pain and Tobacco Dependence

The recently updated U.S. Department of Health and Human Services' Clinical Practice Guidelines for Treating Tobacco Use and Dependence indicates that integrating tobacco dependence interven-

tions into chronic disease management programs may be an effective and efficient way to deliver tobacco use interventions to smokers with comorbid medical conditions (U.S. Department of Health and Human Services, 2008). Hahn et al. (2006) made several recommendations regarding the integration of treatments for smoking cessation and chronic pain, including (a) that tobacco dependence treatment protocols incorporate assessment of pain and contingent referrals for pain management; (b) that pain clinics introduce formal tobacco dependence treatment programs; and (c) that smoking cessation and pain management professionals increasingly seek out and engage collaborative efforts to meet the unique needs of smokers in pain. Clearly, additional research is needed to effectively inform the development and integration of treatments for pain and smoking. Indeed, it is our expectation that future research will instigate collaborative efforts and lead to improved outcomes for persons with comorbid pain and tobacco dependence.

### Summary

The collective societal impact of tobacco smoking and chronic pain is substantial and warrants the existing research investment in their etiology, maintenance, and treatment. Moreover, the evidence of significant comorbidity between the conditions, while producing a combined burden on individuals and systems, also offers insight into the mechanisms underlying their etiology, progression, and maintenance that may ultimately aid in the development of targeted interventions for the respective and combined conditions. This opportunity has recently attracted the attention of researchers and clinicians from multiple disciplines, and modest evidence has emerged, suggesting possible bidirectional causal linkages between pain and smoking. We presented an evolving reciprocal model, which posits that smoking and pain may in fact exacerbate each other via a positive feedback loop. Future research in this emerging area has the potential to refine both theory and application with respect to tobacco smoking, chronic pain, and their comorbid presentation.

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### Correction to Markon et al. (2011)

The article “The Reliability and Validity of Discrete and Continuous Measures of Psychopathology: A Quantitative Review” by Kristian E. Markon, Michael Chmielewski, and Christopher J. Miller (*Psychological Bulletin*, 2011, Vol. 137, No. 5, pp. 856–879) contained a production-related error.

In the Samples section of Meta-Analysis 1: Reliability, third paragraph, the number of studies reporting data on clinical samples is incorrect. The sentence “Four studies included clinical samples, and eight studies included nonclinical samples” should read “Twenty-four studies included clinical samples, and eight studies included nonclinical samples.”

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