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A Reciprocal Model of Pain and Substance Use: Transdiagnostic Considerations, Clinical Implications, and Future Directions

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Abstract

Pain and substance use are highly prevalent and co-occurring conditions that continue to garner increasing clinical and empirical interest. Although nicotine and tobacco, alcohol, and cannabis each confer acute analgesic effects, frequent or heavy use may contribute to the development and progression of chronic pain, and pain may be heightened during abstinence. Additionally, pain can be a potent motivator of substance self-administration, and it may contribute to escalating use and poorer substance-related treatment outcomes. We integrated converging lines of evidence to propose a reciprocal model in which pain and substance use are hypothesized to interact in the manner of a positive feedback loop, resulting in the exacerbation and maintenance of both conditions over time. Theoretical mechanisms in bidirectional pain–substance use relations are reviewed, including negative reinforcement, social cognitive processes, and allostatic load in overlapping neural circuitry. Finally, candidate transdiagnostic factors are identified, and we conclude with a discussion of clinical implications and future research directions.

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INTRODUCTION

Interrelations between pain and substance use are of growing interest to researchers and clinicians from across the medical and behavioral sciences. Although the experience of pain has been linked with the self-administration of various addictive substances for centuries, much contemporary research has focused on opioid use and misuse. Given that the United States is in the midst of an opioid epidemic, the rapidly expanding allocation of scientific attention and economic resources to stem this public health crisis is clearly warranted (Collins et al. 2018). However, an emerging empirical literature also suggests that pain and nonopioid substance dependence are both highly prevalent and comorbid conditions that combine to produce synergistic burdens on individuals, providers, and health-care systems. We conceptualize the interaction of pain and substance use as a prototypical example of the biopsychosocial model, demonstrating the complex interplay among biological, behavioral, cognitive–affective, and physiological–sensory phenomena.

The goals of this review are to synthesize the extant literature on pain and substance use beyond opioids and to propose an integrated reciprocal model that can elucidate clinical implications and guide future research. We focus on nicotine and tobacco, alcohol, and cannabis, as these are the most commonly used substances in the United States (Cent. Behav. Health Stat. Qual. 2017),

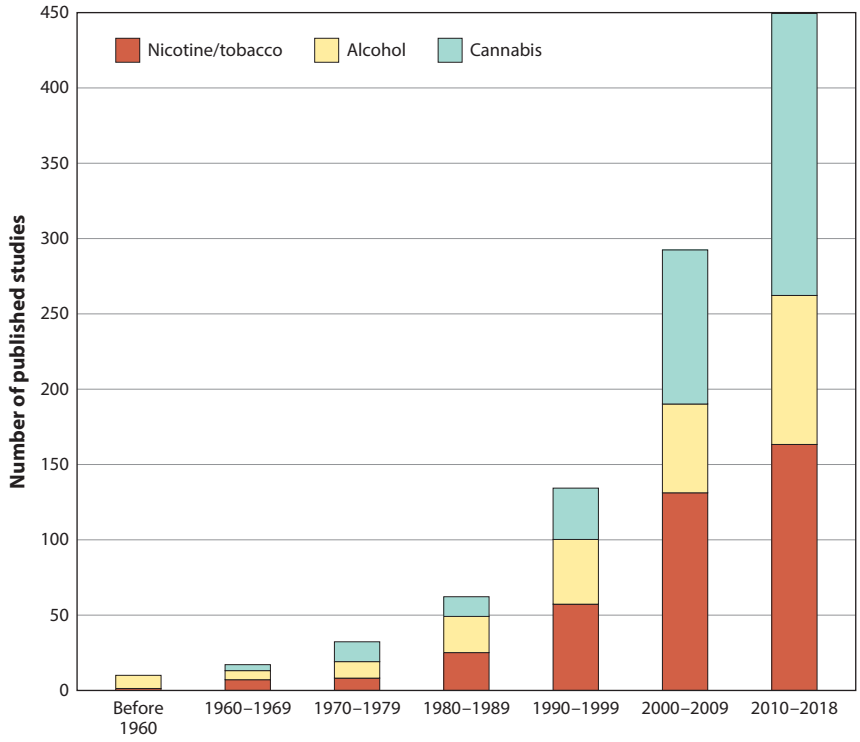

Figure 1

Number of published studies on pain and substance use. Citations were identified through separate searches in PubMed and PsycINFO, and duplicates were removed to generate a total number of published studies in each category. Total citations include primary studies conducted in animals and humans, meta-analyses, and reviews published prior to July 2018. In PubMed, the search terms for nicotine/tobacco were pain[majr] AND (nicotine[majr] OR tobacco[majr] OR smoking[majr]) NOT (cannabis OR marijuana OR angina); search terms for alcohol were pain[majr] AND (alcoholic beverages[majr] OR alcohol drinking[majr]); and search terms for cannabis were pain[majr] AND (cannabis[majr] OR marijuana[majr] OR smoking[majr]) NOT (nicotine OR tobacco OR angina). Angina was an exclusionary term due to features of the PubMed indexing system. Searches in PsycINFO were for the keywords pain AND (nicotine OR tobacco OR smoking) NOT (cannabis OR marijuana); search terms for alcohol were pain AND alcohol; and search terms for cannabis were pain AND (cannabis OR marijuana OR smoking) NOT (nicotine OR tobacco).

and they are the most-studied nonopioid substances in relation to pain. As shown in **Figure 1**, the number of published studies on pain in relation to each of these substances has increased considerably during the past several decades.

The review begins with overviews of pain and substance use, followed by a description of their comorbidity and a brief discussion of guiding theoretical frameworks. We then review studies examining the effects of substance use on pain relative to those examining the effects of pain on substance use. These two lines of empirical inquiry are then integrated to propose a reciprocal model in which pain and substance use are hypothesized to interact in the manner of a positive feedback loop, resulting in greater pain and the maintenance of addiction. Finally, we draw upon this model to emphasize clinical implications and propose directions for future research.

OVERVIEW OF PAIN

Pain is a universal human experience that motivates half of all physician visits in the United States (Turk & Melzack 1992), with an annual economic impact of up to $635 billion in health-care costs and lost productivity (Gaskin & Richard 2012). A multidimensional approach to pain assessment tends to focus on factors such as location, duration, intensity, affect, and degree of physical impairment. Chronic pain is typically defined as pain that persists beyond expected healing time, often lasting longer than 3 to 6 months (Treede et al. 2015). Chronic (noncancer) pain is also differentiated from cancer-related pain, as these conditions diverge in terms of course and etiology (e.g., time frame, levels of pathology, treatment strategies; McMahon et al. 2013). It has been estimated that more than 100 million American adults are encumbered by chronic pain (IOM 2011), with more than 25 million suffering from pain that occurs every day (Nahin 2015).

Pain can be classified as nociceptive, neuropathic, or centralized. Nociceptive pain occurs when tissue damage (e.g., via acute trauma or inflammation) results in signaling from the peripheral (PNS) to the central nervous system (CNS) via intact somatosensory pathways (McMahon et al. 2013). Neuropathic pain results from damage (e.g., via traumatic injury, nerve compression, infection, or toxin exposure) to either the CNS or PNS and accounts for nearly 20% of all chronic pain (Dworkin et al. 2003). Centralized pain occurs when the CNS amplifies sensory signals, resulting in hyperalgesia (i.e., increased responding to noxious stimuli) or allodynia (i.e., pain responding elicited by stimuli that do not typically activate pain circuitry; Woolf 2011), or both. Although pain can be adaptive in the case of acute injury (i.e., by facilitating rest and healing), chronic pain is often considered to be maladaptive in that it may no longer protect against harm or relate to tissue damage (McMahon et al. 2013).

At the neurological level, pain is largely a consequence of noxious stimuli activating nociceptive spinal neurons that project in ascending pathways and transmit pain-related information to various areas of the brain (e.g., forebrain, thalamus, medulla, brain stem; McMahon et al. 2013). These ascending pathways are responsible for amplifying the pain response as the signal moves through the CNS. Conversely, descending pathways, originating in the somatosensory cortex and hypothalamus, synapse onto ascending pathways to inhibit nerve signals and produce pain relief or analgesia, in part via activation of the endogenous opioid system. Thus, heightened sensitivity to pain, or hyperalgesia, can result from increased ascending facilitation, reduced descending inhibition, or both (McMahon et al. 2013). Importantly, the pain experience is also influenced by a variety of affective (e.g., anxiety, depression, anger), cognitive (e.g., pain appraisals, self-efficacy, expectancies), behavioral (e.g., pain avoidance), and genetic factors, with up to 50% of variation in chronic pain development considered heritable (Elman & Borsook 2016, Gatchel et al. 2007, Hocking et al. 2012).

OVERVIEW OF SUBSTANCE USE

Most adults in the United States have used one or more nonopioid substances, with lifetime prevalence estimates of 68% for nicotine and tobacco, 86% for alcohol, and 47% for cannabis (Cent. Behav. Health Stat. Qual. 2017). Nationally representative data further indicate that approximately 14% of American adults currently smoke tobacco cigarettes (Norris et al. 2018), 50% consume at least one alcoholic beverage each month (Schiller et al. 2012), and 9% have used cannabis in the past month (Cent. Behav. Health Stat. Qual. 2017). Unfortunately, regular or excessive use of these substances exerts a significant public health burden. For example, tobacco smoking remains the leading preventable cause of disease and death in the United States (U.S. Dept. Health Hum. Serv. 2014); alcohol engenders a financial burden in excess of $250 billion in annual health-care costs,

lost productivity, and criminal justice costs (Sacks et al. 2015); and initial evidence suggests that cannabis use may be associated with increased costs to health-care systems (Gryczynski et al. 2016).

Substance use is often assessed in terms of frequency, recency, and heaviness of self-administration. Regular substance use can result in tolerance to pharmacological effects and withdrawal when administration ceases (Am. Psychiatr. Assoc. 2013). The presence of tolerance and withdrawal has historically been referred to as substance dependence. Among regular users, self-administration is often motivated by craving or urge to use a substance, which can be elicited by a variety of factors, including decreasing blood serum concentrations, negative affect, and learned associations with drug-related cues (Am. Psychiatr. Assoc. 2013). The presence of a substance-related disorder is determined by diagnostic criteria that reflect a pattern of maladaptive and continued use despite negative consequences. Factors typically considered in the context of substance-related disorders include impaired control (e.g., using larger amounts or over a longer period than intended), social impairment (e.g., failure to fulfill major role obligations at work, school, or home), risky use (e.g., use in situations that are physically hazardous), and pharmacological effects (e.g., tolerance, withdrawal) (Am. Psychiatr. Assoc. 2013). Thus, individuals may use substances with varying frequency and heaviness without meeting the diagnostic criteria for a disorder. In this review, we refer to substance use when discussing frequency or heaviness indicators and note disorder classifications as applicable.

Despite differing pharmacokinetic profiles for nicotine, alcohol, and cannabis, their administration generally results in increased levels of dopamine in the dorsal and ventral striatum and nucleus accumbens (NAc; Volkow et al. 2011), which are central structures in brain reward and reinforcement circuitry (Elman & Borsook 2016). These substances also facilitate the activity of endogenous opioids throughout the neural reward network, which can influence subjective states of pleasure or aversion (Elman & Borsook 2016). Reward neurocircuitry is further modulated by cortical and subcortical structures that influence cognitive–affective processes. For example, the amygdala plays a key part in negative and positive reinforcement derived from substance use, while the medial prefontal cortex (mPFC) is involved in appraisal and decision-making (Elman & Borsook 2016). Approximately 50% of addiction vulnerability is believed to be heritable (Lambert & Kinsley 2011), with evidence of genetic contributions to processes involved in substance metabolism, reward, and the expression of substance-specific receptors in the CNS and PNS (Wang et al. 2012).

CO-OCCURRING PAIN AND SUBSTANCE USE

Prevalence Estimates

The prevalence of co-occurring pain and substance use can be difficult to quantify due to variation in how pain and substance use are operationalized, the settings from which participants are recruited (e.g., clinical versus general population), and the extent to which important third variables are accounted for. Clinical pain patients may also underreport substance use because they are taking or seeking prescription pain medications or due to perceptions of stigma against substance use (St. Marie 2014). Nonetheless, examining co-occurring pain and substance use across populations and settings can yield important base rate information (Elwood 1993).

Accumulating evidence indicates that pain and substance use co-occur with high frequency and that rates of co-occurrence increase as a function of condition severity. For example, nationally representative prevalence estimates indicate that individuals with chronic pain (versus no chronic pain) are twice as likely to smoke tobacco cigarettes (e.g., Zvolensky et al. 2010) and are 50% more likely to endorse lifetime cannabis use (Zvolensky et al. 2011). Among patients in pain clinics,

rates of tobacco smoking (i.e., 24–68% versus 14%; e.g., Michna et al. 2004, Orhurhu et al. 2015) and cannabis use (i.e., 16% versus 8%; Smiley-McDonald et al. 2017) are even higher than those observed in the general population. In addition, greater pain-related physical impairment has been associated with a 23–45% increased likelihood of meeting the criteria for alcohol use disorder (AUD) or nicotine use disorder (NUD; McDermott et al. 2018), and similar patterns are observed when rates of pain are examined as a function of substance misuse. For example, whereas 18% of the general population endorses current moderate–severe pain, that rate increases to 43% among problem drinkers and up to 75% among those with AUD (Brennan & SooHoo 2013, Brennan et al. 2005, Larson et al. 2007).

Third Variables

Several third variables should be considered when examining rates of co-occurring pain and substance use. For example, lower socioeconomic status has consistently been associated with more pain and physical impairment and with greater substance use and related problems (Galea et al. 2004, McMahon et al. 2013). Racial and ethnic minorities are similarly disproportionately burdened by negative consequences of substance use, more severe pain, and greater disability (Campbell & Edwards 2012, Chartier & Caetano 2010, U.S. Natl. Cancer Inst. 2017, Wu et al. 2016). In terms of sex, although substance use is more common among men (Hasin et al. 2016, Jamal et al. 2018, Schiller et al. 2012), women experience more adverse effects of drinking and smoking (e.g., Nolen-Hoeksema 2004, Syamlal et al. 2014) and tend to report pain that is more frequent, severe, and longer lasting (McMahon et al. 2013). Finally, prevalence rates for nicotine use, alcohol use, and chronic pain tend to peak together around middle age (45–65; Jamal et al. 2018, Nahin 2015, Schiller et al. 2012), and older adults remain at high risk for adverse substance use outcomes, even as rates of use typically decrease among individuals older than 65 (e.g., Brennan & SooHoo 2013, Brennan et al. 2011, Nicita-Mauro et al. 2010). While the changing landscape of cannabis use in the United States (including variation in recreational and medical legalization across states) may ultimately result in cohort effects (Schulenberg et al. 2017), current estimates indicate that adults younger than 30 are most likely to meet the criteria for cannabis use disorder (CUD; Hasin et al. 2016).

OVERVIEW OF GUIDING THEORETICAL FRAMEWORKS

This section provides a brief overview of the theoretical frameworks that are commonly applied to both the study of pain and substance use. Constructs and processes that are central to negative reinforcement, social cognitive, and allostatic load perspectives are invoked throughout this review to aid in the interpretation and synthesis of bidirectional pain–substance use relations.

Negative Reinforcement and Self-Medication

Negative reinforcement occurs when a behavior is believed to result in the termination or avoidance of an aversive stimulus, thus increasing the likelihood that it will be repeated in the future. Negative reinforcement models of addiction posit that substance use is largely motivated by the desire to alleviate or avoid aversive internal states (Baker et al. 2004). Further, the self-medication hypothesis specifies a pharmacological link between the use of a given substance and its ability to assuage specific manifestations of distress (Khantzian 1997). The avoidance or alleviation of negative affect is a key component of the negative reinforcement and self-medication perspectives, and it has been hypothesized that using substances to cope with negative affect plays an etiological part

in the development of substance use disorders (Baker et al. 2004). Negative reinforcement is also central to theoretical models of pain. An established four-stage model of pain processing posits that painful sensations produce immediate affective responses (e.g., unpleasantness, negative affect) that, over time, can manifest in terms of pain-related emotional suffering (e.g., depression, anxiety) and drive behavioral pain responses (e.g., efforts to cope) (Wade et al. 1996). The fear-avoidance model further posits that the desire to escape or mitigate pain and pain-related negative affect results in the application of maladaptive behaviors (e.g., avoidance, guarding) that have a key role in the development and worsening of chronic pain (Vlaeyen & Linton 2000).

Social Cognitive Theory

Social cognitive theory (Bandura 1989) emphasizes the role of cognitive processes in human motivation and behavior, including self-efficacy expectancies (i.e., beliefs that one can successfully execute a behavior) and outcome expectancies (i.e., estimates that a given behavior will lead to specific outcomes). Self-efficacy and outcome expectancies can each influence the engagement of cognitive behavioral coping strategies, and coping may be considered adaptive if it improves outcomes or maladaptive if it reduces distress in the short-term but contributes to poorer outcomes over time. Both self-efficacy and outcome expectancies have been linked to the initiation, maintenance, and cessation of substance use (e.g., Metrik & Rohsenow 2013, Shiffman et al. 2000). In the context of pain, self-efficacy for pain management has been associated with improved coping and reduced physical impairment, whereas expectancies that pain will worsen over time have been implicated in the transition from acute to chronic pain (Keefe et al. 2004). Given that expectancies are thought to be influenced by personal experience and social and cultural transmission (Asmundson et al. 2014), it is also possible that individuals who do not use substances or experience pain on a regular basis may still develop substance- or pain-related outcome expectancies.

Allostatic Load

Allostasis is the complex and dynamic process by which physiological systems maintain stability in the face of change (McEwen & Wingfield 2003). Acute perturbations in a physiological system can trigger a cascade of responses, which may include opponent processes (i.e., opposite to the system's initial change) that return the system to its set point (i.e., physiological boundaries for stability) (Elman & Borsook 2016, McEwen & Wingfield 2003). The system may also shift its set point in response to change, thus restoring stability within a new set of parameters. Short-term and infrequent allostatic demands can result in adaptive physiological changes. However, long-term, chronic, or frequent demands can result in persistent physiological imbalances and shifts toward pathological set points (Koob 2003, McEwen & Wingfield 2003). The accumulation of these maladaptive effects is referred to as allostatic load.

In the case of substance use, neural reward circuitry seeks to maintain hedonic homeostasis, and allostatic load occurs when this homeostasis is disrupted by repeated cycles of substance use and disuse, resulting in an imbalance of neurological deficits (e.g., reduced reward) and excesses (e.g., heightened drug salience) (Elman & Borsook 2016). Thus, allostatic load is believed to be a result of, and contributor to, ongoing substance use. Researchers have similarly noted that chronic pain can be considered a "self-amplifying stressor that contributes to allostatic load" (Elman & Borsook 2016, p. 12) and that persistent pain can result in pathological alterations across the systems involved in the pain experience (e.g., sensory, perception, cognition), potentially contributing to a state of heightened pain sensitization and other negative processes (e.g., pain-related suffering) (Simons et al. 2014).

EFFECTS OF SUBSTANCE USE ON PAIN

Acute Analgesic Effects

For thousands of years, the self-administration of addictive substances has been linked with efforts to manage pain (Shealy & Cady 2002). Contemporary studies have focused on how substance use may influence either experimental pain reactivity or self-reported clinical pain. Whereas animal models have consistently demonstrated acute analgesic effects of nicotine, alcohol, and cannabis (Buxbaum 1972, Ibironke & Oyekunle 2012, Sahley & Berntson 1979), the results of human laboratory studies have generally been mixed and may be better understood through meta-analytic approaches that yield pooled effect-size estimates.

For example, a recent meta-analysis showed that nicotine administered via tobacco and other delivery systems (e.g., patch, nasal spray) produced acute analgesic effects that could be characterized as small-to-medium in magnitude (Ditre et al. 2016a). Although these data revealed no evidence of a dose–response effect, moderation analyses indicated that nicotine-induced analgesia may be achieved regardless of current smoking status and that some effects were more robust among samples that included a greater proportion of men.

Similar meta-analytic results were observed for the effects of alcohol on experimentally induced pain, with a mean blood alcohol concentration of 0.08% deemed sufficient to produce small increases in pain threshold and moderate-to-large reductions in pain intensity (Thompson et al. 2017). These data further revealed evidence of a dose–response effect such that additional analgesic benefit was observed for each 0.02% increment in blood alcohol concentration. Similar to findings for smoking, effect-size estimates for pain thresholds were larger in samples with a greater proportion of male participants. In terms of clinical pain, moderate alcohol consumption (versus no alcohol use) has been associated with lower pain severity and less physical impairment among patients with multiple chronic pain conditions (e.g., Gorman et al. 1987, Scott et al. 2018).

Although we are not aware of any meta-analyses examining the effects of cannabis on human experimental pain reactivity, the authors of a recent narrative review observed converging evidence that cannabis can produce acute pain-inhibitory effects among healthy individuals and those with chronic pain (Hill et al. 2017). An influential report by the National Academies of Sciences, Engineering, and Medicine further concluded that there is substantial evidence for plant-based cannabis as an effective treatment for chronic pain (Abrams 2018). It is important to note, however, that the efficacy of cannabis as an acute analgesic remains unclear and understudied, in part due to extensive variation in cross-study legal status, dosing, substance composition (e.g., ratio of tetrahydrocannabinol to cannabidiol), method of administration, and history of substance exposure (Romero-Sandoval et al. 2018). There is also some evidence that cannabis may have less analgesic utility among women (Cooper & Haney 2016).

Mechanisms of acute substance-induced analgesia include direct effects on endogenous opioid and reward neurocircuitry (Ditre et al. 2016a, Egli et al. 2012). Cannabis and nicotine have further been shown to stimulate, respectively, cannabinoid and nicotinic acetylcholine receptors (nAChRs) in the PNS, and each has been implicated in the modulation of ascending pain signals (Kumar et al. 2001, Umana et al. 2013). The degree to which substance use reduces pain in the short term is also likely to be influenced indirectly by a variety of cognitive–affective factors, including mood enhancement and outcome expectancies (Ditre et al. 2011, Lötsch et al. 2018). Indeed, expectancies for pain relief are considered central to descending pain-inhibitory processes (Ossipov et al. 2010), and nicotine and tobacco, alcohol, and cannabis users have all been shown to hold substance-specific outcome expectancies for pain coping and relief (e.g., Ditre et al. 2017, Hill et al. 2017, Zale et al. 2015). The act of substance self-administration may also provide pain relief via behavioral distraction (Hooten et al. 2011).

Abstinence-Induced Hyperalgesia

Consistent with evidence that nonopioid substances confer acute analgesic effects, emerging research suggests that pain sensitivity may be heightened during the early stages of abstinence. Indeed, increased pain reactivity during periods of nicotine and alcohol deprivation has been so consistently demonstrated in the animal literature that hyperalgesia is considered a behavioral marker of nicotine and alcohol withdrawal states. Pain as a component of withdrawal syndromes is further supported by evidence that pharmacological treatments known to mitigate withdrawal symptoms can also attenuate hyperalgesic pain responding (e.g., varenicline for nicotine withdrawal; Bagdas et al. 2018).

In humans, nicotine, alcohol, and cannabis withdrawal tend to be characterized by increased negative affect (e.g., anxiety, depressed mood, irritability), headache pain, and other substance-specific symptoms (Am. Psychiatr. Assoc. 2013). In addition to painful withdrawal symptoms (e.g., headache), human laboratory work provides additional support for the notion that hyperalgesic responding may be a consequence or correlate of substance-related withdrawal syndromes. For example, a recent experimental study showed that daily tobacco smokers who abstained from smoking for 12–24 h (versus continued ad lib smoking) reported greater pain intensity and evinced larger areas of capsaicin-induced neurogenic inflammation and mechanical hyperalgesia (Ditre et al. 2018). Results further indicated that pain ratings were positively correlated with nicotine withdrawal symptoms and that pain sensitivity increased with the duration of smoking abstinence. A similar pattern of findings was observed among African American smokers with chronic pain who rated their pain at two counterbalanced experimental sessions (one following 16 h of smoking abstinence and one following smoking as usual). Specifically, results indicated that overnight smoking abstinence was associated with greater current pain ratings and that abstinence-induced exacerbation of pain was most pronounced among individuals with more severe, persistent, and disabling chronic pain (Bello et al. 2018). Collectively, these findings suggest that increased pain may be a smoking abstinence phenotype.

Initial research conducted among patients seeking treatment for AUD yielded findings that are generally congruent with those in the nicotine and tobacco literature. For example, the results of one experimental study showed that sensitivity to heat pain induction was substantially elevated among patients undergoing acute withdrawal from alcohol relative to those who had achieved longer-term abstinence (2–3 months) and healthy matched controls (Jochum et al. 2010). Follow-up analyses further revealed that within-subject pain reactivity decreased 14 days following admission for treatment, which is commensurate with the idea that abstinence-induced hyperalgesia may be more of a withdrawal effect (i.e., transient change due to abstinence) than a substance disuse or offset effect (i.e., return to levels absent substance-related analgesia; e.g., Hughes 2007). However, it is important to note that because research on nicotine and alcohol has focused on the acute abstinence phases, the time course and duration of abstinence-induced hyperalgesia remain unclear. Also, we are not aware of any studies examining the effects of cannabis abstinence or withdrawal on pain reactivity.

Abstinence-induced hyperalgesia is likely driven, in part, by physiological effects of frequent or heavy substance administration. For example, nAChR availability can modulate pain sensitivity among acutely abstinent tobacco smokers (Cosgrove et al. 2010), and smoking may contribute to changes in inflammatory responding that influence pain reactivity (Bello et al. 2018). Additionally, the downregulation of adenosine receptors and upregulation of L-type calcium channels in response to chronic alcohol administration may mediate alcohol deprivation–induced hyperalgesia (Gatch 2009). Finally, substantial overlap in the reward and pain neurocircuitry may

cross-sensitize pain pathways to allostatic load, which could engender a state of heightened pain during substance withdrawal.

Substance Use as a Risk Factor for Chronic Pain

Despite evidence that widely used addictive substances can reduce pain in the short term, chronic or heavy substance use appears to result in greater pain and physical impairment over time. Indeed, cross-sectional work has consistently demonstrated positive relations between pain intensity and the number of cigarettes smoked per day, levels of alcohol consumption, and frequency of cannabis use (e.g., Hahn et al. 2006, Lawton & Simpson 2009; J.D. Kosiba, L.D. Mitzel, E.L. Zale & J.W. Ditre, manuscript under review). Tobacco smoking has further been identified as a unique risk factor in the onset and progression of several chronically painful conditions, such as chronic back pain (Shiri et al. 2010), rheumatoid arthritis (Sugiyama et al. 2010), and fibromyalgia (Weingarten et al. 2009). There is also some evidence that tobacco cigarette smoking may increase the risk for chronic pain in a linear, dose-dependent fashion (Ditre et al. 2011).

Similar to tobacco smoking, regular and heavy alcohol consumption have been associated with an increased risk for developing chronically painful conditions, including osteoarthritis (Cheng et al. 2000) and pain following musculoskeletal injury (e.g., Sá et al. 2008). Further, chronic pain patients who present for treatment with an AUD have been shown to report more pain and physical impairment than those without an AUD (Holmes et al. 2010). However, unlike smoking, persons who report low-to-moderate levels of alcohol consumption (versus heavy or no drinking) tend to evince lower levels of chronic pain and pain-related disability, which, in turn, has led researchers to hypothesize that relations between alcohol use and chronic pain are likely curvilinear in nature (Larance et al. 2016, Zale et al. 2015). Although we are not aware of any studies that investigated cannabis use as a risk factor for chronic pain, one recent study did show that cannabis users (versus nonusers) reported greater pain severity and consumed a larger quantity of opioid medication following traumatic injury (Salottolo et al. 2018).

The frequent use of addictive substances may contribute to the development and progression of chronic pain via peripheral and central mechanisms, which can be substance specific or common across reward circuitry. For example, nicotine and by-products of tobacco combustion (e.g., CO_2) can cause tissue damage and degeneration (e.g., low back pain) and adverse metabolic and inflammatory processes (e.g., rheumatoid arthritis, cluster headache; Ditre et al. 2011). Alcohol has also been shown to have direct toxic effects on numerous bodily systems, contributing to tissue and bone degeneration (e.g., osteoarthritis), aberrant cellular metabolism (e.g., alcohol-induced pancreatitis), and damage to the PNS and CNS (e.g., alcohol-induced pancreatitis, pain after musculoskeletal injury) (Zale et al. 2015). Further, both heavy nicotine and alcohol use have been shown to cause central opioid deficiency, which has been implicated in aberrant pain processing (e.g., Egli et al. 2012, Shi et al. 2010). Allostatic load on the reward system (due to repeated episodes of substance use and disuse or withdrawal) may also perpetuate allostatic load in overlapping pain neurocircuitry, resulting in a persistent state of increased pain facilitation, decreased pain inhibition, or both (Elman & Borsook 2016). Indeed, a recent functional magnetic resonance imaging study revealed that synchronous activity in the NAc and mPFC (among tobacco smokers with back pain lasting 4–12 weeks) mediated the transition from acute to chronic pain over the 1-year study period and that synchronicity of NAc–mPFC activity decreased following smoking cessation (Petre et al. 2015). This finding provides initial evidence that maladaptive functioning in overlapping pain and reward systems can be attenuated via substance cessation, and it is consistent with initial evidence that smokers who quit using tobacco tend to fare better in pain treatment (Behrend et al. 2012).

EFFECTS OF PAIN ON SUBSTANCE USE

Pain as a Motivator of Substance Use

A growing body of multimethod research indicates that pain can be a potent motivator of nonopioid substance use, that persons in pain may use substances as a means of coping, and that persistent pain and maladaptive coping may escalate substance use over time. For example, laboratory pain induction has been shown to increase the self-reported urge to smoke cigarettes (Ditre & Brandon 2008, Ditre et al. 2010) and consume alcohol (Moskal et al. 2018), with both effects mediated by pain-induced negative affect. Among individuals with chronic pain, data from ecological momentary assessments (EMAs) revealed that increased pain often preceded bouts of smoking (Dhingra et al. 2014), and greater pain unpleasantness ratings among patients with chronic pain have been positively correlated with the motivation to consume alcohol (Lawton & Simpson 2009).

Use of Substances to Cope with Pain

Cross-sectional evidence has consistently suggested that substance use often serves as a means of coping with pain. Indeed, patients have identified pain coping (via distraction from physical pain and pain-related distress) as a primary reason for smoking tobacco (Hooten et al. 2011); approximately one-quarter of persons seeking outpatient treatment for AUD and substance-related disorders report consuming alcohol as a strategy for managing their pain (e.g., Sheu et al. 2008); and recreational cannabis users with chronic pain have been shown to readily endorse the use of cannabis for pain-coping purposes (Ware et al. 2003).

Researchers have previously suggested that the use of substances to cope with pain may hinder the development and engagement of more adaptive pain-coping strategies (Ditre et al. 2011), which, in turn, may contribute to the development and maintenance of both chronic pain and addiction. The use of substances to cope with pain has been associated with greater substance-related problems. For example, prospective evidence indicates that individuals who use alcohol to cope with pain may be more likely to increase their alcohol consumption over time (Brennan et al. 2005). Individuals with comorbid chronic pain and AUD have also been shown to cite pain as a primary reason for starting to misuse alcohol and other substances in the first place (Sheu et al. 2008).

Individuals who endorse the use of tobacco and cannabis for pain coping tend to report greater pain intensity and functional interference (Degenhardt et al. 2015, Patterson et al. 2012), which, in turn, have been linked to heaviness of substance use and the onset of substance-related disorders. For example, the results of a nationally representative prospective survey revealed that greater pain-related functional interference at baseline was associated with an increased likelihood of escalating from nicotine and alcohol use to, respectively, NUD and AUD at 3-year follow-up (McDermott et al. 2018). Among female cannabis users, baseline pain-related functional interference was also associated with a greater likelihood of developing CUD at 3-year follow-up (McDermott et al. 2018).

Pain as a Barrier to Cessation

A rapidly evolving corpus of research further suggests that the presence and severity of pain may influence precessation processes (e.g., self-efficacy, expectancies for quitting), the subjective quality of quit attempts (e.g., perceived difficulty, withdrawal), and lapse and relapse outcomes. Indeed, tobacco cigarette smokers with co-occurring pain (versus no pain) tend to report having less confidence in their ability to quit (Zale et al. 2014) and are nearly 3.5 times more likely to identify pain

as a barrier to smoking cessation (Ditre et al. 2017). Similarly, greater pain has been associated with lower self-efficacy for quitting cannabis (Manning et al. 2018). Smokers with chronic pain (versus no chronic pain) are also more likely to hold expectancies for experiencing more severe nicotine withdrawal during future cessation attempts (Ditre et al. 2016b), and in one study, more than one-third of primary care patients who were deemed at risk for cannabis-related problems reported anticipating difficulty reducing their cannabis use due to a reliance on the substance for ameliorating physical pain and discomfort (Padwa et al. 2014). Finally, pain has been associated with self-reports of more severe nicotine and cannabis withdrawal (Ditre et al. 2016b, Manning et al. 2018).

In terms of cessation outcomes, one prospective randomized controlled trial showed that among veterans undergoing outpatient addiction treatment, those with persistent pain (compared with low pain) evinced poorer rates of abstinence, greater alcohol consumption, and higher total service costs (Caldeiro et al. 2008). Additional prospective work indicates that greater sensitivity to pain may predict relapse to cigarette smoking (Nakajima & al'Absi 2011) and that pain may increase the likelihood of postintervention alcohol consumption and drinking lapses among patients being treated for substance-related disorders in general (Larson et al. 2007) and AUD in particular (Witkiewitz et al. 2015). Although we are not aware of any research examining the effects of pain on cannabis cessation, it has similarly been hypothesized that pain may precipitate relapse among individuals who regularly use cannabis for pain reduction (Hill et al. 2017).

Several mechanisms may account for the effects of pain on substance use, the development of addiction, and relapse following a quit attempt. Consistent with self-medication models of addiction, acute pain relief may negatively reinforce substance use and strengthen expectancies for the utility of substance use as a pain-coping strategy. Researchers have also hypothesized that learned associations between substance self-administration and pain relief may lead to pain becoming a conditioned interoceptive cue that can elicit craving and serves as a proximal antecedent of relapse (Ditre et al. 2011). Finally, persistent pain may increase allostatic load on neural substrates involved in drug-seeking and reward, which, in turn, may facilitate progression to disordered substance use (Elman & Borsook 2016).

COMORBID PSYCHOPATHOLOGY AND TRANSDIAGNOSTIC CONSIDERATIONS

Comorbid Psychopathology

Psychiatric disorders and symptoms, including those related to anxiety, depression, and posttraumatic stress disorder (PTSD), are highly comorbid with both substance use and chronic pain. Individuals with chronic pain are up to four times more likely to meet diagnostic criteria for mood, anxiety, and trauma-related disorders relative to those in the general population (Gureje et al. 2008, McWilliams et al. 2003). There is also evidence that persistent pain may contribute to the severity of anxiety, depression, and PTSD (e.g., Asmundson et al. 2002, Bair et al. 2003). Similarly, individuals with substance-related disorders are two to six times more likely to meet the diagnostic criteria for mood, anxiety, and trauma-related disorders (e.g., Grant et al. 2004, Mills et al. 2006), and the use of tobacco, alcohol, and cannabis has been implicated in the onset of anxiety and depression (e.g., Boschloo et al. 2012, Jamal et al. 2011, Van Laar et al. 2007).

Complex interactions among psychopathology, pain, and substance use are highly relevant to understanding both the effects of substance use on pain and the effects of pain on substance use. Most studies that account for comorbid psychopathology typically do so by including psychiatric symptoms and disorders as covariates in statistical analyses (e.g., Holmes et al. 2010). While

covariation can help to clarify unique variance in pain–substance use relations, this approach does little to explicate the role of psychopathology as a potential mechanism of action. To that end, researchers have begun to examine models of mediation in testing the role of psychopathology in pain–substance use relations. Indeed, there is accumulating evidence that tobacco smoking may contribute to the worsening of depressive symptoms and disorders, which subsequently may lead to greater pain severity and physical impairment (e.g., Goesling et al. 2012, van Hecke et al. 2014). Heightened levels of negative affect and distress that tend to be commensurate with psychopathology are also hypothesized to exacerbate withdrawal and pain experiences, which, in turn, could precipitate relapse and impede future cessation attempts (e.g., Zale et al. 2016).

Candidate Transdiagnostic Factors

Whereas diagnostic categories have utility in the classification and communication of symptom clusters, there is a growing emphasis in the field of clinical psychology on evaluating core constructs that share commonalities across multiple disorders (i.e., transdiagnostic factors; Krueger & Eaton 2015). A transdiagnostic approach is particularly valuable in the study of co-occurring disorders because it can aid in the identification of shared mechanistic processes and better inform the development of novel therapeutic approaches (Krueger & Eaton 2015). In the context of comorbid pain and substance use, leading transdiagnostic candidates include anxiety sensitivity, distress intolerance, pain-related anxiety, and pain catastrophizing.

Anxiety sensitivity (defined as the extent to which one believes that anxiety and related sensations will lead to harmful consequences) has been associated with greater pain and the onset and maintenance of substance-related disorders (Ocañez et al. 2010, Taylor 2014). Individuals with greater levels of anxiety sensitivity are more likely to report using nicotine and alcohol for coping reasons (Stewart et al. 1997) and to endorse conformity motives for alcohol and cannabis use (Comeau et al. 2001). There is also some evidence that anxiety sensitivity is positively and indirectly associated with alcohol problems (through depression symptoms and using alcohol to cope with negative affect; Allan et al. 2015), and that higher anxiety sensitivity may prospectively predict cannabis use during times of greater craving (Buckner et al. 2011).

Emerging evidence also indicates that distress intolerance may have an important role in comorbid pain and substance use. Distress intolerance refers to both the perceived inability to tolerate negative emotional or other aversive states as well as the behavioral act of being unable to withstand distressing states. Research has consistently demonstrated positive associations between distress intolerance and a number of alcohol-, cannabis-, and smoking-related problems (Buckner et al. 2007), and initial evidence suggests that distress intolerance may represent one mechanism by which pain motivates continued substance use. For example, tobacco smokers with co-occurring pain (versus no pain) have reported perceiving themselves as less able to tolerate aversive states (LaRowe et al. 2018), and the inability to tolerate physical discomfort has been positively associated with the frequency of cannabis use among persons with chronic pain (J.D. Kosiba, L.D. Mitzel, E.L. Zale & J.W. Ditre, manuscript under review). Consistent with negative reinforcement models of addiction, it is possible that escape from and avoidance of unpleasant physical and psychological states through substance use is particularly salient among individuals with pain and high levels of distress intolerance (Baker et al. 2004).

Although the face validity of pain-related anxiety (defined as the tendency to respond to pain with anxiety or fear and to engage escape and avoidance behaviors) and pain catastrophizing (defined as the tendency to interpret pain in an exaggerated manner) indicates they are pain-specific processes, there is mounting evidence that both constructs may also be relevant to substance addiction. First, pain-related anxiety is a well-established predictor of poor pain outcomes

(McCracken et al. 1992), and recent work has shown pain-related anxiety to be positively associated with several substance-related outcomes, including heaviness of tobacco use (Ditre et al. 2013, 2015) and the use of nicotine and cannabis to cope with aversive states (Hogan et al. 2010, Patterson et al. 2012). Second, there is prospective evidence that greater pain-related anxiety is predictive of early lapse and relapse among cigarette smokers engaging in a self-guided quit attempt (LaRowe et al. 2017). Likewise, pain catastrophizing has been identified as a mechanism in the effects of pain on the urge to smoke tobacco (Kosiba et al. 2018). Recent research also demonstrates that greater pain catastrophizing may be associated with the use of cannabis for pain management (Sterniczuk & Whelan 2016). We are not aware of any studies that examined pain catastrophizing in the context of pain–alcohol relations.

INTEGRATED RECIPROCAL MODEL OF PAIN AND SUBSTANCE USE

This review synthesizes findings from two lines of empirical inquiry to propose an integrated reciprocal model of pain and substance use (**Figure 2**). In terms of the effects of substance use on pain, we observed evidence that although the administration of nicotine, alcohol, and cannabis can each reduce pain in the short term, substance users are likely to experience increased pain or hyperalgesia when attempting to abstain (perhaps in a manner consistent with substance-specific withdrawal patterns). Moreover, chronic or heavy substance use may serve as a unique risk factor in the development and worsening of chronic pain. In terms of the effects of pain on substance use, we observed converging evidence that pain can be a strong motivator of urge and substance-use behavior, in part via increased negative affect. Consistent with this perspective, pain patients reliably endorse the use of substances to cope with pain, and pain-related processes have been shown to predict relapse following a cessation attempt. We also noted the importance of considering comorbid psychopathology and identified several candidate transdiagnostic factors.

Our conceptualization of pain–substance use relations as being reciprocal in nature was further guided by several theoretical frameworks that help to explain why pain and substance use may interact in the manner of a positive feedback loop to ultimately maintain or exacerbate both conditions over time. First, it is our contention that substance use is negatively reinforced via acute analgesia and the alleviation of abstinence-induced hyperalgesia, which, in turn, may strengthen substance-related outcome expectancies for pain amelioration. To that end, our review noted the relevance of several social- cognitive processes, including substance-related self-efficacy and outcome expectancies, self-efficacy for managing pain, and the development and utilization of adaptive pain-coping strategies. Specifically, we propose that individuals who come to rely on substance use to cope with pain or hold strong expectations that pain will impede cessation will be less likely to quit and more likely to experience deleterious pain outcomes. Second, we hypothesize that as pain and substance use become increasingly chronic, these interrelationships will become more salient and impactful. Finally, consistent with allostatic load conceptualizations of substance use and chronic pain (e.g., Egli et al. 2012, Elman & Borsook 2016), we posit that chronic episodes of pain and substance use can dysregulate the overlapping neural systems responsible for both pain and reward processing. Indeed, allostatic load on these systems, whether caused by pain, substance use, or both, is believed to engender a pathological state that facilitates both pain and drug-seeking behavior (Egli et al. 2012, Elman & Borsook 2016).

CLINICAL IMPLICATIONS

One important implication of these findings is that clinicians and researchers would likely benefit from assessing both pain (e.g., chronic pain status, current pain intensity, degree of physical

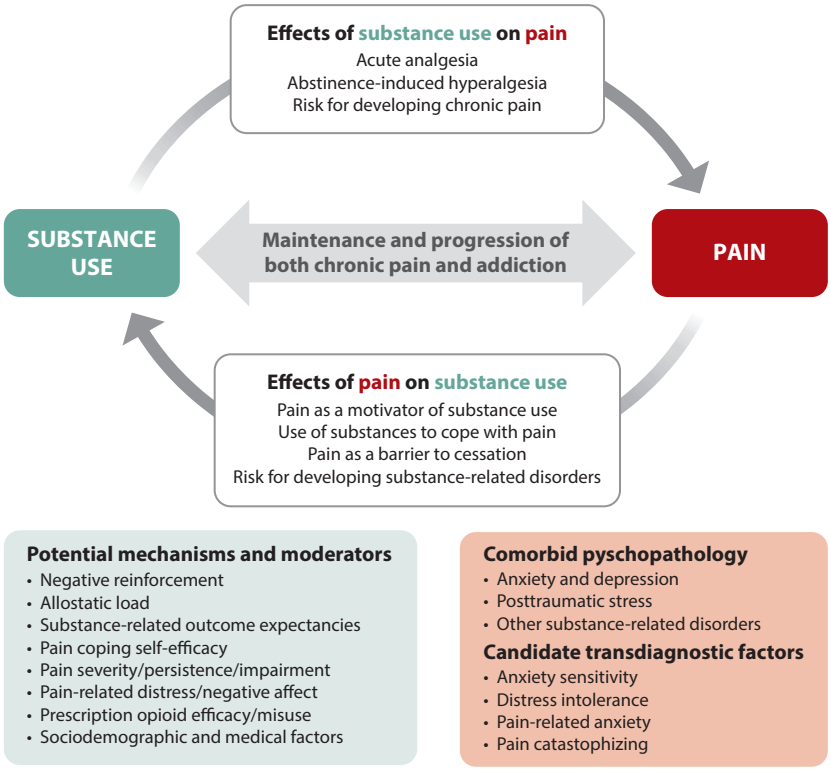

Figure 2

Reciprocal model of pain and substance use. This reciprocal model integrates two lines of scientific inquiry examining associations between pain and the self-administration of nicotine and tobacco, alcohol, and cannabis. In terms of the effects of substance use on pain, substance use has been shown to confer acute analgesia, and abstinence has been shown to produce hyperalgesia. In terms of the effects of pain on substance use, pain has been shown to motivate substance use; pain patients widely endorse the use of substances to cope with pain; and pain has been identified as an important barrier to quitting. We further hypothesize that negative reinforcement and allostatic load processes function as important mechanisms in bidirectional pain–substance use relations to operate in the manner of a positive feedback loop and, ultimately, contribute to the maintenance and progression of both pain and substance addiction. Finally, we highlight several additional mechanisms and potential moderating factors.

impairment) and substance use behaviors when conducting research or providing treatment for either condition. In the context of substance use, pain and related factors should be assessed prior to treatment, monitored throughout, and regarded as potentially important predictors of intervention outcomes (this may be especially important among individuals who hold strong pain–substance use expectancies). Moreover, regular substance users with comorbid pain may be expected to experience a variety of negative pain-related sequelae during the initial phases of quitting (e.g., hyperalgesia), and increased pain during the early stages of abstinence could precipitate relapse. Therefore, abstinence-oriented interventions for nicotine and tobacco, alcohol, and cannabis should account for pain.

It is also important to consider patterns of substance use when evaluating and treating clinical pain. Ongoing substance use could interfere with medical pain treatments (e.g., pharmacological and surgical interventions) via substance-specific (e.g., effects on tissue degeneration

and healing) and general neurobiological effects (e.g., allostatic load). We conceptualize substance use as a maladaptive pain behavior that has the potential to undermine psychosocial pain treatments aimed at improving physical and psychological functioning in the face of pain. Thus, it is imperative for pain treatment to involve the assessment and mitigation of substance use behaviors.

Consistent with our reciprocal conceptualization, we propose that both pain and substance dependence can be usefully addressed via integrated treatment. Such treatments may include psychoeducation regarding interrelations between pain and substance use (e.g., the potential for continued substance use to increase pain and physical impairment) undertaken in an effort to develop discrepancy between current behavior (i.e., continued substance use) and desired pain outcomes. It may also be helpful to challenge pain–substance use expectancies (e.g., expectancies for pain or negative affect relief; Ditre et al. 2010) and to teach more adaptive pain-coping strategies (e.g., relaxation, distraction, mindfulness) prior to encouraging quitting. Indeed, training in pain-coping skills may enhance self-efficacy for quitting, reduce expectations that pain will impede cessation, and ultimately diminish pain-induced motivation to use substances. Training in coping skills may also be paired with other behavioral techniques, such as interoceptive exposure, in which patients are gradually exposed to painful stimulation while being encouraged to use more adaptive coping strategies. Finally, there is initial support for the notion that pharmacological treatments traditionally utilized for the withdrawal syndrome (e.g., varenicline in the context of smoking cessation) should be considered for their potential to ameliorate abstinence-induced hyperalgesia (Bagdas et al. 2018).

Transdiagnostic interventions (i.e., protocols that apply the same underlying principles across disorders) that target factors implicated in comorbid pain and substance use also offer substantial promise. Indeed, transdiagnostic interventions are efficient at treating comorbid conditions (versus sequentially treating each disorder) because they facilitate the generalization of treatment effects in a more timely and cost-effective manner (e.g., McEvoy et al. 2009). Our review identified several transdiagnostic factors that are hypothesized to maintain and exacerbate pain–substance use relations, including anxiety sensitivity, distress tolerance, pain-related anxiety, and pain catastrophizing. Interventions designed to target these factors may help to break repeated cycles of pain and substance self-administration, perhaps by reducing tendencies to escape or avoid pain via substance use.

It may also be useful to employ electronic treatment delivery. For example, computer-based interventions are portable, adaptable, and cost effective; can be delivered to a large number of patients by nonspecialized care providers; and are able to reach patients who would not otherwise engage with traditional models of care (e.g., Portnoy et al. 2008). Likewise, mobile health interventions offer opportunities for real-time monitoring and feedback, and their dynamic nature allows for adaptations to changing goals, motivation, and needs over the course of treatment (e.g., Litvin et al. 2013). Mobile health interventions could be utilized in real time to intervene on pain-induced urge to use a substance, perhaps by providing expectancy challenges, motivational exercises, or cues for alternative coping strategies when patients indicate heightened pain ratings.

DIRECTIONS FOR FUTURE RESEARCH

Although clinicians and researchers have been interested in pain–substance use relations for decades, this remains a nascent domain of scientific inquiry. Additional research is needed to better understand pain–substance use covariation, momentary and longer-term pain–substance use effects, and the bidirectional processes by which pain and substance use become increasingly interrelated over time. Special consideration should be given to identifying and accounting for relevant

third variables (e.g., sociodemographic factors), potential mediators and moderators (e.g., negative affect, and pain and substance use expectancies), comorbid psychopathology, and emerging transdiagnostic factors (e.g., anxiety sensitivity, distress intolerance, pain-related anxiety, and catastrophizing). Researchers should also continue to examine these processes among special populations that evince pain- and substance-related health disparities (e.g., low-income and minority individuals), as well as among individuals living with medical conditions in which pain is a prominent feature (e.g., persons living with HIV; Weinberger et al. 2018).

There is also a need to further quantify the prevalence of co-occurring pain and substance use by more consistently and comprehensively assessing pain among individuals who use or misuse various substances (e.g., type of pain, severity, impairment, persistence, and duration) and by assessing substance use among individuals with persistent pain (e.g., type of substance, frequency and heaviness of use, route of administration, other substance use, and the presence of substance-related problems and disorders). Despite increasing interest in pain–substance use relations, it is our observation that many providers and clinical researchers who work in the areas of pain and addiction remain largely unaware of how these conditions may impact their own study or treatment outcomes. Moreover, we have observed that when examining relations between pain and a single substance (e.g., nicotine and tobacco), the use of other substances (e.g., cannabis) is often not considered. Failure to account for pain- and/or other substance-related factors could result in incomplete statistical models, the misattribution of causal relationships (e.g., if pain or substance use is not adequately distributed across groups following randomization), and a reduced capacity for identifying potentially salient predictors of treatment outcomes.

Prospective and EMA studies are also needed to establish the natural time course of co-occurring pain and substance use, as well as temporal precedence in pain–substance use processes. For example, EMA can be employed to examine pain as a proximal antecedent of substance self-administration (e.g., Dhingra et al. 2014) and to test the effects of substance use and abstinence on pain reporting in more naturalistic (i.e., nonlaboratory) environments and among individuals with clinical pain disorders. EMA would further allow for the real-time assessment of social cognitive processes, as well as variations in negative affect and comorbid psychopathology symptoms, in relation to pain intensity and episodes of substance use. Future prospective research should also investigate the effects of substance cessation on pain reporting and physical impairment over time (Volkman et al. 2015) and, conversely, pain status and severity as predictors of substance-related withdrawal and cessation outcomes (e.g., Bello et al. 2018).

Recent advances in experimental pain assessment, particularly via quantitative sensory testing (e.g., McMahon et al. 2013), should increasingly be applied to the study of pain and substance use. Novel techniques that move beyond static measures of pain threshold and tolerance are capable of clarifying underlying neurological mechanisms and may enhance our understanding of how pathological functioning in one system (e.g., pain processing) can influence another (e.g., reward neurocircuitry). For example, more dynamic laboratory pain paradigms that assess temporal summation allow for inferences regarding central sensitization and pain facilitation, whereas the assessment of conditioned pain modulation allows for inferences regarding centrally mediated pain-inhibitory processes (e.g., McMahon et al. 2013). Quantitative sensory testing paradigms could also be used to estimate the magnitude and duration of substance-induced analgesia and abstinence-induced hyperalgesia. Balanced placebo designs would be especially helpful in differentiating pharmacological and expectancy effects in pain–substance use outcomes.

Although our reciprocal model posits that the magnitude of pain–substance use interrelations is likely to increase as both conditions worsen and/or maintain over time, it is also important to consider that pain is a universal human experience and that most US adults have used at least one

substance in their lifetime. Thus, we caution against focusing future research on clinical samples and instead recommend that these processes be explored in a variety of populations, including healthy controls and individuals with limited or intermittent pain and substance-use experiences. Additional research is also needed to test whether analgesic and hyperalgesic effects vary by heaviness, frequency, and duration of use across substances. In the case of cannabis, for example, researchers have speculated that acute analgesia may be optimized within specific therapeutic dosing windows or perhaps even diminish with increased use and the development of tolerance (D'Souza et al. 2016).

In addition to further informing our understanding of mechanisms in pain–substance use comorbidity, future research is sorely needed to leverage this knowledge and directly address the burden experienced by individuals who are living with both chronic pain and substance addiction. Researchers have recently begun developing and testing novel tailored and integrated pain–substance use interventions, and a continued investment in clinical trials and cost-effectiveness studies is warranted. Clinical, epidemiological, and laboratory data are essential to aid in the identification of potentially valuable treatment components and modifiable social cognitive and transdiagnostic factors. Important questions remain with regard to how and when these factors can be best addressed in the context of integrated treatment. For example, given initial evidence that pain-related anxiety is predictive of lapse and relapse to tobacco smoking (LaRowe et al. 2017), future interventions should examine the utility of reducing pain-related anxiety prior to a quit attempt.

Finally, future research should examine the role of pain medication use and misuse in bidirectional pain–substance use relations. Regular or heavy substance use may induce cross-tolerance and cross-sensitization to prescription opioids, which, in turn, may reduce their effectiveness and increase the risk for developing opioid-related disorders (e.g., Robinson & Berridge 2003, Turk et al. 2008). The use of prescription pain medications may also modulate associations between pain and the self-administration of nonopioid substances. For example, opioid use may enhance craving for other substances, increase the salience of substance-related cues (e.g., pain), and ultimately make nonopioid substances more rewarding and harder to give up (Robinson & Berridge 2003). Indeed, tobacco smokers with chronic pain have reported increased craving for cigarettes and greater cigarette consumption when using prescription opioids (Hooten et al. 2011). Analgesia derived from prescription pain medications could also decrease the motivation to seek out and self-administer other substances for pain management. Finally, although a rapidly emerging literature suggests that individuals with chronic pain may substitute medical cannabis for opioids, the overall safety and efficacy of medical cannabis regimens remains indeterminate (Hill et al. 2017).

CONCLUSIONS

The study of the interrelations between pain and substance use represents an area of clinical and experimental research that has garnered increasing scientific attention due to the high rates of comorbidity and the substantial combined public health impact. This review integrated two parallel lines of empirical inquiry (the effects of substance use on pain and the effects of pain on substance use) to propose a reciprocal model in which pain and substance use are hypothesized to interact in the manner of a positive feedback loop, resulting in the maintenance and progression of both conditions over time. Future research in this emerging domain has the potential to explicate bidirectional pain–substance use effects, refine theoretical perspectives, and, ultimately, inform the development of novel treatments for the millions of individuals who suffer from both chronic pain and substance addiction.

SUMMARY POINTS

1. Reciprocal relations between pain and substance use are hypothesized to interact in the manner of a positive feedback loop, resulting in the maintenance and exacerbation of both conditions over time.
2. Although nicotine and tobacco, alcohol, and cannabis can each reduce pain in the short term, frequent or heavy use may be a risk factor for the progression of chronic pain, and attempting to abstain from using these substances could result in hyperalgesia or increased sensitivity to pain during the early stages of quitting.
3. Pain has been shown to motivate substance use; pain patients readily endorse the use of substances to cope with pain; and pain has been identified as an important barrier to cessation.
4. Substance use may be negatively reinforced via acute analgesia and the alleviation of abstinence-induced hyperalgesia, and the allostatic load on neural systems responsible for both pain and reward processing may engender a pathological state that facilitates both pain and drug-seeking behavior.
5. Individuals who either come to rely on substances to cope with pain or hold strong expectations that pain will impede cessation may be less likely to quit and more likely to experience deleterious pain outcomes.
6. Comorbid psychopathology (e.g., anxiety, depression, posttraumatic stress) and candidate transdiagnostic factors (e.g., anxiety sensitivity, distress intolerance, pain-related anxiety, pain catastrophizing) likely have important roles in pain–substance use relations.

FUTURE ISSUES

1. Although clinical and empirical interest in pain–substance use relations have increased during the past 70 years, this remains a nascent domain of scientific inquiry.
2. Future research should examine pain–substance use covariation, momentary and longer-term pain–substance use effects, and the bidirectional processes by which pain and substance use become increasingly interrelated over time.
3. Future work should also identify and account for relevant third variables, comorbid psychopathology, and emerging transdiagnostic factors in pain–substance use relations.
4. Prospective and ecological momentary assessment studies are needed to establish the natural time course and temporal precedence in pain–substance use processes.
5. Recent advances in experimental pain assessment, particularly quantitative sensory testing, should increasingly be applied to the study of pain and substance use.
6. Clinicians and researchers are advised to assess and account for pain- and/or substance use–related factors when assessing and treating either condition.
7. Clinical trials and implementation studies are sorely needed to develop and test integrated pain–substance use treatments. Transdiagnostic approaches (i.e., treatments that target underlying constructs common across disorders) and electronic delivery (e.g., mobile health applications) are particularly promising.

8. Future work should consider the role of prescription pain medication use and misuse in pain–substance use relations.

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