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The Affective Dimension of Pain as a Risk Factor for Drug and Alcohol Addiction

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Abstract

Addiction, or substance use disorder (SUD), is a devastating psychiatric disease composed of multiple elemental features. As a biobehavioral disorder, escalation of drug and/or alcohol intake is both a cause and consequence of molecular neuroadaptations in central brain reinforcement circuitry. Multiple mesolimbic areas mediate a host of negative affective and motivational symptoms that appear to be central to the addiction process. Brain stress- and reinforcement-related regions such as the central amygdala (CeA), prefrontal cortex (PFC), and nucleus accumbens (NAc) also serve as central processors of ascending nociceptive input. We hypothesize that a sensitization of brain mechanisms underlying the processing of persistent and maladaptive pain contributes to a composite negative affective state to drive the enduring, relapsing nature of addiction, particularly in the case of alcohol and opioid use disorder. At the neurochemical level, pain activates central stress-related neuropeptide signaling, including the dynorphin and corticotropin-releasing factor (CRF) systems, and by this process may facilitate negative affect and escalated drug and alcohol use over time. Importantly, the widespread prevalence of unresolved pain and associated affective dysregulation in clinical populations highlights the need for more effective analgesic medications with reduced potential for tolerance and dependence. The burgeoning epidemic of prescription opioid abuse also demands a closer investigation into the neurobiological mechanisms of how pain treatment could potentially represent a significant risk factor for addiction in vulnerable populations. Finally, the continuing convergence of sensory and affective neuroscience fields is expected to generate insight into the critical balance between pain relief and addiction liability, as well as provide more effective therapeutic strategies for chronic pain and addiction.

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Keywords

addiction; amygdala; corticotropin-releasing factor; nucleus accumbens; pain; prefrontal cortex

Introduction

Drug and alcohol addiction, also termed substance use disorders (SUDs; DSM-5, 2013) represent devastating diseases (Leshner, 1997). The interaction of abused substances with brain circuitry has long been a focus of intense research generously supported by national governments, private foundations, and individuals. A lack of truly effective treatments for addiction has driven neuroscientists to generate an abundance of data related to drug-induced neuroadaptations as well as innovative conceptualizations of the transition from recreational drug use to addicted states. This transition is considered driven by a combination of tolerance and sensitization processes within specific neural circuitry following repeated or excessive drug exposure (Koob & Le Moal, 1997). For example, tolerance to the rewarding or otherwise intake-limiting effects of drugs coincides with a sensitization of incentive motivational processes to drive the pursuit and use of abused substances (Self, 1998). Consequently, individuals suffering from addiction will often report a phenomenon termed “chasing the dragon” where the seemingly maximal hedonic value of the initial drug experience is sought after but never recapitulated with subsequent use. Importantly, drug and alcohol exposure is also postulated to activate brain anti-reward systems that are considered vital for the adaptive process of reward homeostasis under normal conditions (Koob & Le Moal, 2008). However, repeated or heavy drug use potentiates negative affective conditions (e.g., anxiety, dysphoria) over time, representing a cumulative allostatic load challenging homeostasis and ultimately driving excessive intake and continued relapse via negative reinforcement mechanisms (Edwards & Koob, 2013). Historical investigations focused on negative motivational processes have delineated specific neuroanatomical and neurochemical substrates that promote a variety of addiction-related behaviors (Edwards & Koob, 2010). More recently, conceptualizations of opioid (Shurman, Koob, & Gutstein, 2010) and alcohol (Egli, Koob, & Edwards, 2012) addiction as chronic pain disorders have emerged, highlighting the negative affective dimension of pain as a central component to facilitate and maintain these devastating conditions. Valuable insights into the biobehavioral mechanisms that determine the analgesic efficacy and abuse-related properties of drugs and alcohol have provided a foundation for future investigations into the neurobiological intersection of pain and addiction.

Pain in clinical populations: risk for affective disorder and addiction

Chronic pain is a leading cause of long-term disability and affects over 100 million Americans (Institute of Medicine, 2011), more than diabetes, heart disease, and cancer combined. Treatment options largely rely on prescription analgesic drugs, primarily opioid-based, with incomplete success. Healthcare professionals must also balance the vital need to administer opioid analgesics with the risk for diversion, misuse, and addiction (Fields, 2011; Volkow & McLellan, 2011). It is important to note that addiction to prescription opioids in the context of proper analgesic use is rare (Fishbain, Cole, Lewis, Rosomoff, & Rosomoff,

2008) although addiction liability is increased in individuals with a history of illicit alcohol or drug misuse. Additionally, chronic pain patients can still exhibit substantial craving for prescription opioids even in the absence of addiction, with affective state playing an important role in this relationship (Wasan et al., 2012). Finally, in addition to prior drug abuse, a history of mood disorder may place individuals at risk for prescription opioid misuse (Wasan et al., 2007).

Unfortunately, chronic pain is intimately associated with the manifestation of affective disorders such as major depression and generalized anxiety disorder (Demyttenaere et al., 2007; Elman, Borsook, & Volkow, 2013; Yalcin & Barrot, 2014). Increasing recognition of this troubling relationship has led some to label this interaction as the depression-pain syndrome (Chopra & Arora, 2014; Lindsay & Wyckoff, 1981), with the incidence of depression among chronic pain patients found to range from 30–85%, depending on the study setting (Bair, Robinson, Katon, & Kroenke, 2003; Dworkin & Gitlin, 1991; Maletic & Raison, 2009; Ruoff, 1996). Furthermore, depressed patients report more pain symptoms than the general population, with an average of 65% of patients experiencing one or more pain complaints (Bair et al., 2003). Another crucial dimension of this relationship is the extent of pain and depression severity, with reciprocal correlations increasing as the severity of either condition grows (Currie & Wang, 2004; Gerrits et al., 2012; Haley, Turner, & Romano, 1985; McWilliams, Cox, & Enns, 2003). While there does not appear to be differences in the overall incidence of chronic pain or depression based on age or sex, men and women differ in the relationships among depression, general activity, and chronic pain. For example, in female patients, depression most closely relates to their self-reported pain severity, whereas depression correlates more closely to decreased activity levels in males (Haley et al., 1985). Such distinctions warrant more preclinical investigation into sex differences that moderate nociceptive signaling (Mogil & Bailey, 2010) and pain-induced affective dysregulation. This is particularly important given the considerable differences in analgesic responsiveness between men and women (Loyd & Murphy, 2014).

Although the most common manifestation of chronic pain-related affective disorder is depression, anxiety and fear are also commonly experienced and may result in even greater psychiatric morbidity (Dersh, Polatin, & Gatchel, 2002). In a population-based study, the prevalence of anxiety disorders was 35% in persons with chronic pain compared with 17% in a healthy control population (McWilliams et al., 2003). The associations between chronic pain and anxiety disorders (e.g., panic disorder, agoraphobia, and PTSD) also appear to be even stronger than associations between pain and depression. Contrary to pain-related depression, most anxiety disorders are present prior to the onset of pain, and such anxiety-prone patients may develop significant distress and functional disability as the result of pain-related fear and catastrophizing (Dersh et al., 2002; Knaster, Karlsson, Estlander, & Kalso, 2012).

Pathologies associated with intermittent pain episodes are also linked with devastating and costly affective complications. For example, patients suffering from sickle cell disease (SCD), a condition characterized by severe acute pain crises on top of chronic somatic and neuropathic pain beginning in childhood and persisting throughout life, tend to have elevated rates of depression and anxiety disorders (Cepeda, Yang, Price, & Shah, 1997;

Hasan, Hashmi, Alhassen, Lawson, & Castro, 2003; Levenson et al., 2008). Affective dysregulation in SCD patients is similar to other medical conditions associated with chronic pain (Bennett, 1994; Ericsson et al., 2002; Kato, Sullivan, Evengård, & Pedersen, 2006; Widmer & Cadoret, 1978), and these patients subsequently have longer lengths of hospitalization for treatment of pain (Myrvik, Burks, Hoffman, Dasgupta, & Panepinto, 2013) as well as higher overall healthcare usage and medical costs as compared to similar patients without psychiatric diagnoses. Data from the Pain in Sickle Cell Epidemiology Study (PiSCES) indicated that approximately one-third of SCD patients surveyed met criteria for alcohol abuse (Levenson et al., 2007). Interestingly, alcohol abusers reported greater pain relief from opioids compared to those who did not use alcohol.

In the absence of physician awareness and vigilance, chronic pain-associated affective disorders may remain unrecognized or misdiagnosed and subsequently may be inappropriately or inadequately treated. Although somatic symptoms of pain are a common marker of depression that are often initially addressed with a primary care physician, studies suggest that depressed patients presenting with pain symptoms are unlikely to receive an accurate diagnosis (Bridges & Goldberg, 1985; Kirmayer, Robbins, Dworkind, & Yaffe, 1993). Misdiagnosis of pain-related affective disorders carries significant implications for acute and long-term management and treatment outcomes. For example, patients with depressive symptoms who also report pain are often treated with opioid analgesics rather than antidepressants (Doan & Wadden, 1989), potentially increasing the risk of opioid addiction without adequately treating the underlying issue. Alternatively, patients who receive concomitant treatment for both pain and depression, either through antidepressant medications or psychotherapy, have better outcomes compared to those treated for pain alone (Teh, Zaslavsky, Reynolds, & Cleary, 2010), displaying an alleviation of depression as well as decreased pain symptoms (Kroenke et al., 2009).

Pain, affective dysregulation, and addiction in preclinical animal models

Given the overwhelming evidence connecting chronic pain and emotional disruption in humans, nociceptive physiology is now routinely investigated beyond the sensory dimension at the preclinical level (Yalcin, Barthas, & Barrot, 2014). Unresolved pain can be considered a form of chronic, inescapable stress (Blackburn-Munro & Blackburn-Munro, 2001), and a significant effort has been put forth to understand the underlying neurobiological mechanisms that represent the link between persistent pain states and the gradual enhancement of negative affective-like behaviors in rodents (Fig. 1; Yalcin et al., 2011). Anxiogenesis in the context of chronic pain has been modeled in several laboratories. In a seminal study by Narita and colleagues, male C57BL/6J mice underwent either sciatic nerve ligation (SNL) to produce neuropathic pain, or hindpaw injection of Complete Freund's Adjuvant to generate a state of chronic inflammatory pain (Narita et al., 2006). Anxiogenic-like effects were observed 4 weeks post-surgery (and not sooner) in both pain models, as indicated by a significant decrease in time spent in the lighted compartment of the light-dark box, and a significant decrease in time spent in the open arms of the elevated plus maze. Importantly, this study also linked pain-induced magnification of negative affective-like behavior with changes in opioid signaling in the amygdala. For example, persistent inflammatory pain produced reductions in mu- and delta-opioid receptor function while

increasing kappa-opioid receptor (KOR) function. This latter neuroadaptation is in accordance with the effects of dynorphin/KOR signaling in anxiety- and depression-like behavior (Van't Veer & Carlezon, 2013).

Interestingly, pain can also activate mesolimbic dynorphin/KOR systems to reduce dopamine levels (Narita et al., 2005), and this effect can blunt morphine reward. Moreover, pain reduces the ability of opioids to potentiate brain reward as measured by intracranial self-stimulation of the ventral tegmental area (Ewan & Martin, 2011). These effects are consistent with the role of acute dopamine tone in opioid reward and reinforcement (Nestler, 1996), and also in agreement with the abundance of clinical data indicating that the majority of pain patients prescribed opioids (i.e., those without a history of drug abuse) do not appear to be at increased risk of addiction (Fishbain et al., 2008). As described above, an imbalance of opioid signaling in the amygdala during chronic pain (i.e., enhanced KOR activity) was hypothesized to protect the majority of pain patients from the transition to addiction (Narita et al., 2006). However, it remains unknown how repeated or tonic activation of KOR (or other stress systems) over an extended history of pain and in combination with regular drug use would influence addiction processes. Interestingly, animals in a state of chronic pain following SNL exhibited a rightward-shift in heroin self-administration, with low doses failing to support self-administration in favor of higher doses associated with anti-hyperalgesic efficacy (Martin, Kim, Buechler, Porreca, & Eisenach, 2007). Such a preference for higher opioid doses is consistent with tolerance, a central DSM-5 criterion for SUD. Thus, while pain-mediated aversion and compromised dopamine signaling may antagonize acute drug reward in the near term, significant evidence suggests that enhanced dynorphin/KOR signaling (Bruchas, Land, & Chavkin, 2010) and a repeatedly compromised dopamine system (George, Le Moal, & Koob, 2012) facilitate the development of addiction in the long term. In this regard, Kreek and colleagues have constructed an intriguing conceptualization of the evolution of dynorphin/KOR processes and potential treatment strategies at various stages of the addiction process (Butelman, Yuferov, & Kreek, 2012). Interestingly, KOR antagonism via nor-BNI prevents the escalation of alcohol drinking (Walker & Koob, 2008) and heroin self-administration (via actions in the nucleus accumbens, Schlosburg et al., 2013) in rats. KOR antagonism also reduces anxiety-like behavior associated with drug withdrawal (Chartoff et al., 2012; Kallupi et al., 2013), but unfortunately does not reduce hyperalgesia in heroin-dependent animals, and even produces hyperalgesia in non-dependent animals (Schlosburg et al., 2013). This latter effect is consistent with the analgesic effects of endogenous dynorphin signaling and should be considered when evaluating the balance of therapeutic benefits and side effects of KOR antagonism in humans.

In addition to heroin dependence, several other animal models of addiction have consistently demonstrated a gradual development of hyperalgesia following excessive exposure to alcohol, morphine, and nicotine (McGinn & Edwards, *in press*). Notably, escalated intake of psychostimulants such as cocaine does not produce hyperalgesia (Edwards et al., 2012). An interaction of nociceptive signaling with multiple neurochemical stress systems appears to play a critical role in the manifestation of drug-induced hyperalgesia, including a contributory role for glucocorticoids (Dina et al., 2008) and corticotropin-releasing factor

(CRF; Apkarian et al., 2013). CRF is a key regulator of the endocrine hypothalamic-pituitary-adrenal (HPA) axis and a central neuropeptide that mediates both adaptive and maladaptive stress responses (de Kloet, 2013; Zorrilla, Logrip, & Koob, 2014). Importantly, antagonism of CRF1 receptors (CRF1Rs) alleviates hyperalgesia associated with dependence on morphine (McNally & Akil, 2002), heroin (Edwards et al., 2012), nicotine (Baiamonte et al., 2014; Cohen et al., 2013), and alcohol (Edwards et al., 2012). Consistent with these findings, several lines of preclinical pain research have found chronic pain-induced increases in forebrain CRF levels. For example, Herman and colleagues discovered that rats experiencing chronic neuropathic pain induced by chronic constriction injury of the sciatic nerve displayed increased CRF and glucocorticoid receptor (GR) mRNA expression in the central amygdala (CeA) at approximately 3 weeks post-surgery (Ulrich-Lai et al., 2006). Another group with a similar experimental design confirmed this neuroadaptation by finding increases in CRF immunoreactivity in the CeA (Rouwette et al., 2011). Importantly, these neuroadaptations were not present in the paraventricular nucleus of the hypothalamus, indicating a sensitization of central GR/CRF-related stress signaling (dissociated from HPA-axis activity) in chronic pain states. CRF has been implicated in a number of psychiatric disorders (Aubry, 2013; Koob, 2009), suggesting that this system may act as a critical mediator between pain and maladaptive negative affect in association with drug addiction. These effects could occur via CRF's downstream regulation of the dynorphin/KOR system described above (Bruchas et al., 2010; Land et al., 2008). However, in contrast to chronic KOR antagonism, chronic CRF1R blockade was shown to both reduce escalation of heroin intake and concomitantly alleviate heroin-induced hyperalgesia (Park et al., 2013). These results suggest that opioid exposure produces a sensitization of CRF function that may drive both opioid-induced hyperalgesia and escalation of opioid use, and that hyperalgesia represents a unique reinforcer with a distinct neurochemical signature that stands apart from other negative affective dimensions.

Sensitization of pain-related negative affect in addiction

Nevertheless, chronic pain is highly comorbid with anxiety and depressive disorders, and it is becoming more evident that a bidirectional relationship exists whereby a chronic pain state can influence the development of mood disorders, while the severity of a mood disorder such as major depression can influence the reported intensity of pain. This close interaction indicates a sensitization between and within negative affective states to exacerbate psychiatric disorders. Interestingly, a popular working model of addiction posits a sensitization of processes related to incentive salience and motivation (Self & Nestler, 1995; Steketee & Kalivas, 2011; Wolf, 1998), and suggests that drug-induced sensitization of brain mesocorticolimbic systems that attribute incentive salience to drugs and drug-associated stimuli are the primary cause of addiction (Robinson & Berridge, 1993). These systems can generate excessive incentive motivation ("wanting") for drugs in susceptible individuals in what may be described as a pathological positive reinforcement process. In a somewhat similar fashion, opioid drugs are hypothesized to generate a pro-nociceptive sensitization (Célèrier, Laulin, Corcuff, Le Moal, & Simonnet, 2001) that may enhance negative reinforcement processes to foster addiction (Park et al., 2013).

Moreover, cross-sensitizing interactions of stress and mesolimbic dopamine system circuits (regulated by glucocorticoid and CRF systems) have been hypothesized to promote addiction liability (Bonci & Borgland, 2009; Burke & Miczek, 2014; Edwards & Koob, 2010; Marinelli & Piazza, 2002). Incentive sensitization effects are extremely long lasting, which is one of the key factors in addicts being vulnerable to relapse even after years of abstinence. In a similar fashion, stress and related negative affective conditions can generate considerable craving to promote relapse well into abstinence (Goeders, 2003; Mason, Shaham, Weiss, & Le, 2009; Sinha, 2007). Importantly, hyperalgesia remains present in formerly opioid-dependent individuals for up to several years, and negative affective stimuli further exacerbate hyperalgesia in this population (Carcoba, Contreras, Cepeda-Benito, & Meagher, 2011). In turn, individual pain sensitivity would appear to predict opioid misuse (Edwards et al., 2011). Ren, Shi, Epstein, Wang, & Lu (2009) specifically investigated whether pain sensitivity could act as a factor driving opioid craving after protracted abstinence. Former opioid-dependent individuals exhibited reduced pain tolerance even after several months of abstinence. Interestingly, opioid cue-induced craving was indeed predicted by individual pain sensitivity. Moreover, this sensitivity was based not on pain perception but on pain-induced distress, suggesting the critical role of the negative emotional translation of pain in relapse compared to the sensory dimension of nociception *per se*.

Chronic pain and nociceptive hypersensitivity may promote drug craving and relapse via alterations in synaptic plasticity within brain reinforcement circuitry, essentially via an extension of the “central sensitization” theory of pain originally proposed by Woolf (Woolf, 1983, 2011). In accordance with neuroadaptations described in the previous section, converging lines of evidence suggest that pain-induced levels of CRF modify the electrophysiological properties of nociceptive CeA neurons (Bernard, Huang, & Besson, 1990) to promote pain sensitization (Neugebauer, Li, Bird, & Han, 2004). Rats placed in a state of arthritic inflammatory pain exhibit increased CeA excitability that is alleviated by CRF1R antagonism (Ji & Neugebauer, 2007). Moreover, the emergence of anxiety-like behavior in this arthritis model is also reduced following either systemic or intra-CeA CRF1R blockade (Ji, Fu, Ruppert, & Neugebauer, 2007), indicating that CRF signaling may underlie the transformation of pain into negative affect within the nociceptive CeA (Egli et al., 2012; Shurman et al., 2010). At the same time, non-pain-related activation of CeA CRF1R signaling also augments nociceptive responsiveness (Ji, Fu, Adwanikar, & Neugebauer, 2013), potentially providing an interactive mechanism for stress and anxiety to influence pain severity. Downstream of CRF1R activation, extracellular signal-regulated kinase (ERK) signaling in the CeA has also been demonstrated to promote pain sensitization (Fu et al., 2008), and activation of this pathway in the CeA is intimately involved in various addiction-related behaviors such as excessive drug and alcohol intake, withdrawal, and relapse (Edwards, Graham, Whisler, & Self, 2009; Lu, Koya, Zhai, Hope, & Shaham, 2006; Sanna, Simpson, Lutjens, & Koob, 2002; Zamora-Martinez & Edwards, 2014). Finally, in addition to the CeA, preclinical models have revealed sensitizing pain-induced plasticity within the anterior cingulate cortex (ACC; Fuchs, Peng, Boyette-Davis, & Uhelski, 2014), a subregion of the prefrontal cortex (PFC). Chronic pain states enhance multiple markers of excitatory glutamatergic neurotransmission within the ACC (Wu et al., 2005, 2008; Zhao et

al., 2006). Interestingly, Cao and colleagues (2009) discovered a role for ACC ERK activity in the induction and expression of negative affective-like behavior in the context of inflammatory pain. Overall, an abundance of preclinical evidence suggests that reducing ERK signaling in the CeA and ACC represents an attractive therapeutic strategy to reduce the risk of unresolved pain developing into affective disorders and addiction. Provided the limited safety profile of systemic kinase inhibition, this effect might be more readily achieved via antagonism of central pro-nociceptive systems that couple to the ERK pathway. In addition to CRF1Rs, the nociceptin receptor represents another possible target in this regard (Chen, Huang, & Yu, 2008). However, nociceptin appears to promote both supraspinal pro-nociceptive as well as (putatively beneficial) anxiolytic processes (Witkin et al., 2014), potentially confounding its therapeutic utility at the interface of pain and addiction.

Conclusions and future directions

Given the almost inseparable nature of pain and stress, future preclinical modeling of the interaction of chronic pain and addiction should incorporate strategies and lessons learned from combined stress and addiction models (Hopf, Sparta, & Bonci, 2011; Logrip, Zorrilla, & Koob, 2012), including the contribution of individual differences and conditioning factors. For example, animals exposed to a single traumatic stressor exhibit hyperalgesia over subsequent days (Roltsch et al., 2014), while an enhanced and stable avoidance of a traumatic stress-paired environment in only a subset of these animals (representing a model of post-traumatic stress disorder; Whitaker, Gilpin, & Edwards, 2014) predicts post-stress escalation of alcohol drinking (Edwards et al., 2013). These results suggest that specific combinations of negative affective symptoms may interact in vulnerable individuals to promote excessive drug and alcohol intake.

Like traumatic stress, various pain conditions also produce a conditioned place aversion (CPA) to formerly pain-paired environments (Johansen & Fields, 2004; Minami, 2009). The CPA procedure represents a valuable extension of evoked, reflexive methods commonly used to measure nociceptive hypersensitivity. Porreca and colleagues successfully used the CPA procedure to reveal tonic pain conditions and assay the efficacy of treatments that alleviate the aversive quality of pain and thereby act as rewards (King et al., 2009) via elevated dopamine signaling in the NAc (Xie et al., 2014). The emergence and utilization of operant measures that gauge the reinforcing dimensions of pain and analgesia are expected to bridge the fields of sensory and affective neuroscience (Navratilova & Porreca, 2014). This methodology will likely be instrumental in fostering a greater understanding of the delicate balance between pain relief and addiction liability, and will hopefully lead to the development of more effective therapeutic strategies for chronic pain and addiction.

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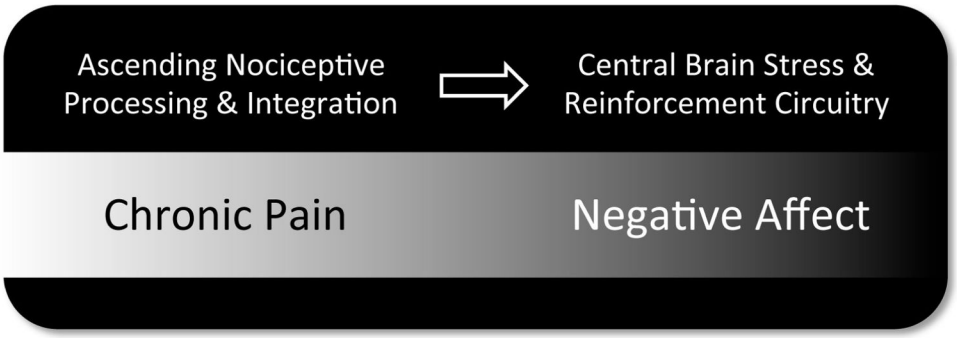

Fig. 1.

Persistent pain conditions (e.g., neuropathy, arthritic inflammation) originate peripherally but interact with ascending nociceptive circuitry in the spinal cord and brain via central sensitization mechanisms. Translation of chronic pain into negative affect occurs as a consequence of increased nociception-driven activity within central brain stress and reward/reinforcement circuitry, including the central amygdala. Importantly, pain-induced affective dysregulation may contribute to the transition to addiction in vulnerable individuals with a history of drug abuse. Medications targeting neuroadaptations associated with chronic pain- and drug-induced hyperalgesia may represent effective therapeutic strategies for drug and alcohol addiction.