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## Neuroinflammation—a co-occurring phenomenon linking chronic pain and opioid dependence

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### Abstract

Chronic pain is a disease that encompasses both sensory and emotional elements. Opioids are highly effective analgesics because they target both of these elements, by inhibiting pain pathways and alleviating negative affect (including depression) by engaging reward or hedonic pathways. Unfortunately, chronic opioid use is limited by the development of unwanted side effects, such as tolerance, hyperalgesia, and abuse liability. Thus, the challenge of providing effective pain treatment while minimizing these unwanted side effects is an ongoing issue with significant clinical and societal impact. In this review, we posit that neuroinflammation within the central nervous system is a shared phenomenon between chronic pain and opioids that contributes to pain sensitization and negative affect. The implications for pain progression, addiction liability, and alternative treatment strategies are discussed.

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Pain is a multidimensional experience encompassing both sensory and emotional elements. The emotional component, or how much the pain is 'bothersome', significantly impacts the quality of life of the sufferer and has been argued to be the greatest metric for quality of life. Chronic pain may be considered an epidemic in our society affecting 25% of Americans, and quality of life of chronic pain patients is reported to be lower than other disorders such as heart failure, renal failure, and depression [1]. Opioid analgesics are highly effective and the most commonly prescribed class of medications in the United States, with a significant portion of these prescriptions dedicated to long-term opioid therapy. However, the conundrum of providing effective pain treatment while minimizing prescription opioid abuse has become a major challenge. There are alarming statistics on therapeutic opioid misuse, although the abuse of therapeutic opioids is largely a result of diversion (obtaining opioids

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#### Conflict of interest

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from family and friends) [2]. In the United States in 2013, over 37% of all drug overdose deaths could be attributed to prescription opioids. The United States Center for Disease Control and Prevention (CDC) reported, for the first time, that drugs surpassed the leading cause of death in 16 states over car accidents. However, not everyone exposed to opioid analgesics becomes addicted to their medication. The question that needs to be addressed is what makes patients susceptible to opioid misuse. We will argue that a commonality of chronic pain and opioid misuse is dysphoria and the occurrence of neuroinflammation. This immune response contributes to dysphoria and drives negative affect by disrupting mesocorticolimbic dopaminergic circuitry responsible for reward and motivation. Dampened reward circuitry is a causative factor in many psychiatric illnesses including depression, and neuroinflammation also exacerbates depressive symptoms in these illnesses. We posit that both chronic pain and chronic opioids induce neuroinflammation in limbic brain structures leading to the genesis of negative affective states (anxiety and depression). Thus, chronic opioid regimens may exacerbate the negative affect associated with chronic pain, and patients taking opioids to treat pain may become reliant on opioids to alleviate this negative affect, making them susceptible to opioid misuse and consequently the transition to addictive-like behaviors.

### **Are chronic pain patients at risk for opioid addiction?**

Opioid prescription abuse occurs in both chronic pain populations and in individuals that obtain opioids from friends and/or family, where misusers may migrate to heroin (as a cheaper source). It is therefore disturbing that physicians prescribe opioids for patients with chronic pain with little (if any) assessment of the level of risk for medication abuse [3], although new CDC guidelines are enforcing change.

The high abuse rates of therapeutic opioids have fueled a strong debate on the treatment practices of using prescription opioids and whether pain is a major factor in addiction susceptibility. Epidemiological reports and case studies have suggested that pain is 'protective' against the development of opioid dependence and addiction where rates of abuse are low at 3.75% even when considering patients with prior illicit drug use [4]. This argument is validated by preclinical studies showing that opioids are self-administered only at doses that reverse mechanical hypersensitivity in a model of neuropathic pain and that anti-inflammatory drugs reduce opioid consumption in a model of chronic inflammatory pain [5][for review, 5]. However, others argue that opioid misuse and aberrant drug related behavior in chronic pain patients range from 21 to 29% [6], and iatrogenic (physician-induced) addiction may be as high as 26% [2]. Relevant to this argument are data showing that chronic pain patients that are opioid tolerant (defined as >60 mg morphine equivalent) or exhibit high catastrophizing, distress intolerance and/or impulsivity scores have greater likelihood of abusing their opioid medication [7,8]. The claim that chronic pain increases opioid addiction-like behaviors is supported by preclinical research where persistent inflammatory pain (complete Freund's adjuvant, CFA) caused animals to self-administer more heroin than non-pain animals [9] or reduced the number of conditioning sessions required to produce drug-conditioned place preference [10]. However, these studies cannot differentiate between the negative reinforcement associated with pain relief from the hedonic reward produced by the opioid, which obfuscates conclusions regarding motivated behavior

within the context of chronic pain. Similarly, although animals experiencing CFA-induced inflammatory pain maintained intravenous self-administration of morphine (0.2 mg/kg/infusion, but not 1 mg/kg/infusion) at the same levels as control animals, rats in pain demonstrated significantly greater morphine-seeking behavior during withdrawal [11]. Thus, it remains unclear if chronic pain patients have higher susceptibility to prescription opioid misuse and addiction. However, chronic pain patients with comorbid depression are more likely to develop opioid abuse than non-depressed patients, which is correlated with higher opioid doses and longer duration of use [12]. Thus, as with non-chronic pain populations, there are recognized susceptibilities for developing addictive behaviors. Identifying the endophenotypes that lead to opioid misuse susceptibilities, and the neurobiology that encodes them, should be a current focus of addiction medicine (Figure 1a). The research reviewed above indicates that underlying affect or motivational states have significant influence on abuse liability, and thus function within emotional or affective circuits should be considered when contemplating the impact of pain on addictive behaviors.

### **Overlapping and interacting brain regions contribute to opioid addiction and the subjective experience of pain**

Seeking pain relief and seeking reward are two motivational states that engage overlapping brain structures and circuitry involved in affect and salience (e.g. anterior cingulate cortex, dorsal and ventral striatum, habenula, and amygdala (Figure 1b)). The mesocorticolimbic circuit plays a central role in motivational processes, and incorporates dopaminergic neurons in the ventral tegmental area (VTA) that project to the nucleus accumbens (NAc). Dopamine release within this circuit acts as an incentive salience signal underlying reinforcement learning produced by environmental (e.g. sex, food), rewarding drugs, as well as aversive stimuli. VTA dopamine neurons respond to salient, motivational stimuli by burst firing, which is suppressed by tonic GABA input. VTA GABAergic neurons and other GABAergic input from the rostromedial tegmental nucleus (RMTg), NAc, and ventral pallidum, tonically inhibit dopamine neuronal activity. Opioids produce reinforcing effects, in part, by inhibiting GABAergic tone on VTA dopamine neurons (disinhibition). Indeed, rodents will self-administer opioids directly into the VTA [13] and opioids locally injected into the VTA will produce a conditioned place preference [14,15]. Pain relief is also reinforcing and engages dopaminergic circuitry. For example, local administration of a peripheral nerve block in a rodent model of persistent pain stimulates dopamine release in the NAc and produces a place preference [16]. Thus, untangling the motivational salience of opioids, which are both analgesic and rewarding, in the context of pain is a challenging task. Moreover, the analgesic and rewarding effects of opioids engage overlapping circuits. Above we discussed the evidence that supports a role for dopamine release in the reinforcing properties of opioids. Next we present evidence that demonstrates engagement of the mesocorticolimbic dopamine system contributes to opioid analgesic efficacy, as well.

The pain experience is comprised of three components: a sensory component that relays information regarding location and intensity, a cognitive component, and an affective component influenced by context, culture, and experience. Opioids are effective in diminishing both the sensory and affective components of pain. For example, post-operative

patients receiving opioid analgesics will describe being satisfied with their level of pain because it does not bother them although they often still report ‘feeling’ pain. The ability of opioids to dissociate the emotional component of pain is partly caused by their ability to release dopamine in the NAc, hence alleviating the affective dimension of pain. Preclinical models have demonstrated this concept directly where morphine suppression of formalin-induced (but not tail flick) pain was attenuated by destruction of VTA dopaminergic neurons [17] and morphine injected directly into the VTA or NAc produced analgesia in this same pain model [18], suggesting that on-going or persistent pain states engage dopaminergic circuitry, and activation of the system is sufficient to produce analgesia. However, dopamine release in the NAc has also been proposed to facilitate pain [19]. This discrepancy may be caused by the topographical organization of heterogeneous dopaminergic inputs within the NAc and differential activation of specific medium spiny projection neuronal populations. Indeed, optogenetic stimulation of dynorphin-expressing cells in the ventral NAc shell elicits aversive behaviors via kappa opioid receptor activation, and in contrast photo-stimulation of dorsal NAc shell dynorphin cells induces a kappa opioid receptor-mediated place preference [20\*\*]. How VTA dopamine neurons projecting to the NAc encodes aversion or reward remains opaque, but there is evidence that plasticity within the NAc is contributive to both chronic pain states and chronic opioids [21,22].

### **Hypodopaminergia driven by neuroinflammation is a shared phenomenon between chronic pain and opioid addiction**

Depression and mood disorders are co-morbid conditions common in both chronic pain and opioid addiction patient groups. The prevalence of depression in chronic pain patients ranges from 30 to 80%, depending on the pain etiology. The relevance of this co-morbidity is highlighted in that chronic pain is second only to bipolar disorder as the major cause of suicide among all medical illnesses [23,24]. Similarly, opioid dependent patients have a high incidence of depression. Indeed, opioid use in the absence of pain has been shown to induce a protracted abstinence syndrome [25,26], and can increase the likelihood of major depressive episodes [27]. There is also recent evidence that long-term prescription opioid use is associated with both new onset and recurrence of depression [28], as well as enhances the risk of developing treatment resistant depression [29\*]. This is particularly concerning as the short-term benefits of opioids that alleviate the sensory and affective symptoms of pain may lead to longer duration of opioid use, which theoretically could increase risk of adverse outcomes, including depression. The interface of pain and opioid addiction is complex given the high comorbidity of pain with negative affect and that opioids provide relief of both negative affect and pain. One, therefore, cannot rule out the possibility that reported opioid misuse in the chronic pain population may be due, in part, to pain patients taking opioids to relieve the negative affect associated with chronic pain that may be exacerbated by opioid withdrawal, and where the relief of dysphoric states becomes an important driver of opioid seeking behavior. In support of this theory, clinical studies investigating subjective reporting in electronic diaries obtained from heroin addicts identified feeling sad as a driver of opioid craving [30], whereas subjects on buprenorphine or methadone maintenance continued therapy because they want to feel ‘normal’ [31,32]. We have recently argued that the opioid abstinence syndrome and the anxiogenic and negative affective states that evolve following

abstinence [25,33] are likely salient factors for learning that opioids relieve negative affect, which drives subsequent addictive behaviors [34\*].

The mechanisms underlying the high incidence of mood disorder co-morbidity are poorly understood. However, one commonality to chronic pain, depression, and opioid addiction is diminished or perturbed function of mesolimbic dopaminergic circuitry. A common endophenotype in both chronic pain and opioid addicts is anhedonia with a lack of appreciation of natural rewards such as sex and food. An elegant review recently argued that reward deficiency and anti-reward systems contributes to the vulnerability of suicidal acts and behaviors in chronic pain populations [24](8). There exists convincing evidence that dysfunction of mesolimbic circuitry (including dopamine neurotransmission) precipitates mood disorders and impairs motivated behavior [35,36]. Opioid dependent states induce hypo-function of the VTA-NAc mesolimbic dopaminergic projections [37]. This is evidenced by the loss of conditioned place preference produced by intra-VTA administration of a selective mu opioid agonist DAMGO [38], an effect also evident in (opioid naïve) chronic pain states [14]. Preclinical and human subject research have identified strong correlations between dysfunction of mesolimbic circuitry and chronic pain [39](13). We have shown that drug (morphine and cocaine)-evoked release of dopamine is blunted in chronic pain states [14]. This decrease in release was correlated with a blunting of reward assessed by conditioned place preference to both cocaine and opioids that we show may be caused by an increase in GABAergic neuronal excitability in the VTA. We proposed that GABA tone on dopaminergic neurons was increased by the occurrence of chronic pain leading to a blunting effect of dopaminergic transmission. Subsequently, others have reported that chronic pain causes a decrease in basal dopamine release within the NAc, and this decrease in release was positively correlated with a decrease in VTA dopaminergic neuronal firing [40\*\*]. However, a blunting of dopaminergic transmission is not always observed with reports that pain causes an increase in dopamine neuronal burst firing that is associated with an increase in basal release [41]. Differences in outcomes may be caused by the topographical organization of heterogeneous dopamine neurons, where cells in the dorsal and ventral VTA are inhibited or excited by noxious electrical stimuli, respectively [42]. Topographical organization of the VTA also exists in the rostral caudal axis and likely dictates projection target and function [43]. Moreover, opioid agonists can have bidirectional effects in the VTA, whereby locally applied opioid agonists can activate or inhibit different populations of VTA dopamine neurons with unique projection targets [44,45], and may contribute to the diversity of behavioral responses recorded following manipulation of VTA dopamine output. Nevertheless, imaging studies on human volunteers and chronic pain patients suggest that perturbation of the mesolimbic-cortical dopaminergic reward circuitry contributes to chronic pain syndromes, including altered activity within the VTA [46]. Moreover, a high prevalence of chronic pain is common in disorders linked with deficits in the dopamine system, including disorders of mood and affect, substance abuse, and Parkinson disease.

The mechanism underlying the hypofunction of dopaminergic circuitry in either opioid dependent states or chronic pain remains elusive; however, one commonality that may link these disorders is an increase in brain-derived neurotrophic factor (BDNF). In models of depression, including social defeat, BDNF is up-regulated in the NAc [47]. Additionally,

phasic, but not tonic, activation of VTA dopamine neurons projecting to the NAc, but not the prefrontal cortex (PFC), induced susceptibility for a depressive phenotype, which was associated with increased BDNF in the NAc [48]. Selective deletion of BDNF from the VTA-NAc circuitry prevented the development of social defeat stress [47]. It must be emphasized that an increase in BDNF in the NAc contributing to depression is a site-specific effect. In the hippocampus, many pharmacotherapies that alleviate depressive symptoms elevate BDNF, and social defeat stress model of depression decreases BDNF in the hippocampus [49]. Several clinical studies have implicated the BDNF Val66Met polymorphism as associated with severity of depressive symptoms [50] and risk of bipolar disorder [51]. However, a recent genome-wide association study (GWAS) did not identify the BDNF locus as associated with depression in a large Chinese cohort [52]. BDNF is also a critical modulator of VTA dopamine function in opioid dependence. Intra-VTA administration of BDNF was shown to be a negative modulator of opioid reward and blunted morphine-evoked dopamine release [53]. Opioid withdrawal elevated BDNF mRNA and protein levels in the VTA [54]. Interestingly, BDNF serum levels were altered in heroin-dependent patients after 26 weeks of abstinence, which correlated with protracted withdrawal symptoms (appearance of anxiety and depressive symptoms) [33]. Similarly, serum BDNF was proposed as a biomarker or determinant of bipolar disorder or depressive symptoms [55,56]. BDNF is the most abundant growth factor in the brain and while it is primarily derived from neurons, microglia, the resident immune cells in the brain, also have the capacity to release BDNF [57]. In the spinal cord, microglial-derived BDNF was responsible for the pain sensitization associated with chronic opioid exposure [58]. We posit that a commonality in both chronic pain and opioid misuse is occurrence of neuroinflammation in the basal ganglia and other limbic structures that contributes to the hypofunction of the mesolimbic system that may be a common pathophysiology triggering the incidence of depression in both disorders (Figure 1c).

The central innate immune system, comprised of microglia and astrocytes, is “activated” in response to a number of events associated with chronic pain, including trauma to peripheral or spinal nerves. Indeed, spinal cord glia are intrinsically involved in cell-to-cell signaling pathways producing chronic pain [57], at least in males [59]. While much of what we know about glial contribution to chronic pain emanates from studies in the spinal cord, more recent reports have found evidence for widespread glial activation throughout pain and affective brain circuits [60,61]. Thus, activated glia are poised to contribute to both the sensory, cognitive, and emotional aspects of chronic pain. The innate immune system is also reported to modulate opioid-induced effects within the central nervous system and may account for the reduced efficacy of opioids in the treatment of neuropathic pain. Critical experiments in support of this hypothesis observed that drugs disrupting glial functioning prevented and/or reversed pain behavior in a number of chronic pain models and improved opioid effectiveness [62]. Chronic opioids, similar to chronic pain, induces neuroinflammation and increases the production of pro-inflammatory cytokines such as IL-1b and TNF $\alpha$  throughout the neuroaxis. Cytokines can affect glutamatergic homeostasis (17) that leads to morphine tolerance and opioid-induced hyperalgesia. Blocking glial activation interferes with the development of many of the unwanted side effects associated with chronic opioid use such as hyperalgesia, without interfering with analgesia [58]. We

hypothesize that the mechanism by which immune cells increase pain and impair reward circuitry is shared between chronic pain and chronic opioid conditions. Pertinent to this thesis, BDNF released from spinal microglia and subsequent down-regulation of the  $K^+/Cl^-$  co-transporter KCC2 is at least partially responsible for pain hypersensitivities in a chronic pain model [63]. Moreover, both chronic pain and chronic opioids activate microglia and increase BDNF expression in the VTA, a phenomenon that impairs mesolimbic dopamine function and reward behavior [14,54]. Inhibiting neuroinflammation recovered opioid-evoked DA release and reward behavior in chronic pain animals [14]. Similarly, the antibiotic ceftriaxone, which inhibits microglial activation, normalized the effect of morphine on NAc shell D1 and D2 neurons [64]. Thus, glial activation in the mesocorticolimbic system is a common pathophysiology triggering the genesis of depression in both chronic pain and opioid dependence. Indeed, inhibitors of neuroinflammation (including the tetracycline microglial inhibitor minocycline) were shown to be effective adjunct therapy in major depressive disorders [65] and improved the affective dimension of chronic neuropathic pain without altering its intensity [66\*].

## Conclusion

Despite significant advances in our understanding of the mechanisms underlying chronic pain, the basis for its persistence and resistance to most medical treatments are not known. One of the mechanisms proposed to underlie synaptic plasticity pertinent to the development and persistence of chronic pain includes neuronal–glia interactions, particularly products released from activated microglia. Opioids are often prescribed to manage chronic pain, though their side effect profile, including hyperalgesia, opponent processes and addiction liability, raise questions regarding their clinical utility over the long term. In this review, we explore the evidence that both chronic pain and chronic opioids engage similar neuroimmune mechanisms in the brain and spinal cord that contribute to pain sensitization and negative affect. This suggests that the use of opioids may, paradoxically, exacerbate the progression of chronic pain by enhancing the immune responses, an idea that is supported by both preclinical and clinical reports. Moreover, both chronic pain and chronic opioids promote neuroinflammation in limbic brain structures leading to the genesis of negative affective states. This negative affect may increase the likelihood of opioid misuse and addictive-like behaviors in the chronic pain population. Therapies that restore function in reward circuitry, such as inhibitors of neuroinflammation, may be effective co-therapies to enhance the analgesic efficacy of opioids and restore affect to mitigate addiction liability in the chronic pain population.

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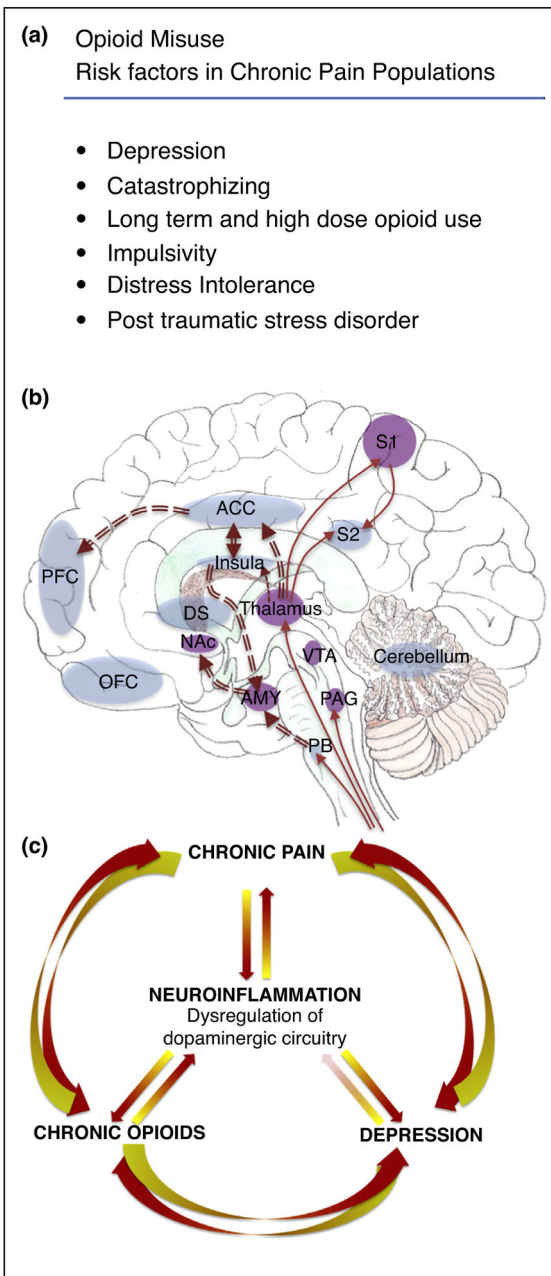


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**Figure 1.** Overlapping neuroanatomical and functional circuitry involved in chronic pain and opioid misuse. Neuroinflammation occurs in mesolimbic circuitry important for reward and motivation. **A.** Risk factors identified for opioid misuse in chronic pain populations. **B.** Chronic pain and chronic opioids induce neuroinflammation in brain regions associated with sensory and affective components. Red solid line arrows indicate sensory pain pathways. Red double line arrows indicate affective component of pain pathways. Purple brain regions denote where changes in neuroinflammation was detected by protein or mRNA of Iba-1 (a marker of microglia), cd11b (marker of microglia) or pro-inflammatory cytokines. Many structures overlap with opioid reward/reinforcement and negative affect/aversion such as the

anterior cingulate cortex (ACC), prefrontal cortex (PFC), insula, thalamus, nucleus accumbens (NAc), and amygdala (AMY). C. Schematic cartoon of the central role neuroinflammation has in producing dysregulation of dopaminergic circuitry in many psychiatric disorders including chronic opioid use, chronic pain and depression. Note in panels B and C, the absence of purple shading does not reflect that neuroinflammation is absent in these structures, but rather many of these regions have not been examined. DS: dorsal striatum, OFC: orbitofrontal cortex, PAG: periaqueductal grey, PB: parabrachial nucleus, S1: primary somatosensory cortex, S2: secondary somatosensory cortex, VTA: ventral tegmental area.

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