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Review

Review

From Pleasure to Pain, and Back Again: The Intricate Relationship Between Alcohol and Nociception

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Abstract

Aims: A close and bidirectional relationship between alcohol consumption and pain has been previously reported and discussed in influential reviews. The goal of the present narrative review is to provide an update on the developments in this field in order to guide future research objectives.
Methods: We evaluated both epidemiological and neurobiological literature interrogating the relationship between alcohol use and pain for the presence of significant effects. We outlined studies on interactions between alcohol use and pain using both self-reports and objective experimental measures and discussed potential underlying mechanisms of these interactions.
Results: Epidemiological, preclinical and clinical literature point to three major interactions between alcohol use and pain: (a) alcohol use leading to hyperalgesia, (b) alcohol use moderating pain and hyperalgesia and (c) chronic pain as a risk factor predisposing to alcohol relapse. Neurobiological studies using animal models to assess these interactions have transitioned from mostly involuntary modes of experimenter-controlled alcohol administration to self-administration procedures, and increasingly indicate that neuronal circuits implicated in both withdrawal and anticipation stages of alcohol use disorder also have a role in chronic pain. Mechanistically, alterations in GABA, glutamate, the corticotropin-releasing factor system, endogenous opioids and protein kinase C appear to play crucial roles in this maladaptive overlap.
Conclusions: Many of the principles explaining the interactions between alcohol and pain remain on a strong foundation, but continuing progress in modeling these interactions and underlying systems will provide a clearer basis for understanding, and ultimately treating, the damaging aspects of this interaction.

INTRODUCTION

Physicians recognized the ability of alcohol to act as an analgesic agent thousands of years ago and offered it to patients for this purpose during medical procedures (Horn-Hofmann *et al*., 2015). The more general idea that pain and alcohol use are intertwined is substantiated by epidemiological studies showing that alcohol use disorder (AUD) is often comorbid with chronic pain (for reviews, see Egli *et al*., 2012; Apkarian *et al*., 2013; Witkiewitz and Vowles, 2018). For example, older problem drinkers report increased disruption in daily activities because of pain and more frequent alcohol use to manage pain compared with non-problem drinkers (Brennan *et al*., 2005). Over half of individuals seeking treatment for an AUD report significant recurring pain, with a greater prevalence in women (63%) compared with men (54%) (Boissoneault *et al*., 2018). Chronic pain is also a strong predictor of relapse in problem drinkers (Egli *et al*., 2012; Witkiewitz and Vowles, 2018). Thus, the relationship between

alcohol use and pain appears to be bidirectional: on one hand, alcohol intake modulates pain, and on the other hand, acute and chronic pain influence alcohol-related behaviors.

The comorbidity of AUD and chronic pain is likely a manifestation of common neuronal circuits and neurochemical mechanisms (Egli *et al*., 2012; Apkarian *et al*., 2013; Witkiewitz and Vowles, 2018). Given the growing sophistication of neuroscience methodologies and the increased attention to pain management as a consequence of the ongoing opioid epidemic (Rudd *et al*., 2016; Yeung *et al*., 2017), the goal of this review is to provide an update on current understanding of the relationship between alcohol use and pain in order to guide future research objectives. We outline the mechanisms regulating excessive alcohol use and hyperalgesia, highlight the overlapping neural circuits involved in the different phases of addiction and chronic pain and touch on major molecular mechanisms. Finally, we outline missing information on the interactions between alcohol and pain, so that readers can draw conclusions on where gaps need to be filled.

OVERLAPPING DYSFUNCTION IN AUD AND PAIN

AUD is defined as a chronic relapsing brain disease characterized by compulsive alcohol use, loss of control over alcohol intake and negative emotional state when not using alcohol (American Psychiatric Association, 2013). In 2017, ~20.2 million adults aged 18 years or older were diagnosed with a substance use disorder. Among all adults diagnosed with a substance use disorder (including AUD and illicit drug use disorder), 4 of 5 are diagnosed with AUD, as compared with 3 out of 10 diagnosed with an illicit drug use disorder (Lipari and Van Horn, 2017). Moreover, AUD has a 29% lifetime prevalence (Grant *et al*., 2015) and only a 35–40% long-term remission rate (Finney and Moos, 1991). AUD prevalence in men has long been greater than that in women, but the number of women diagnosed with AUD is increasing (Agabio *et al*., 2017; Grant *et al*., 2017).

While multiple theories have been proposed to explain the development of addiction, including AUD (Wise and Bozarth, 1987; Robinson and Berridge, 1993; Koob and Le Moal, 2008; Nutt *et al*., 2015), the opponent process theory of motivation highlights the critical importance of a motivational shift in drinking behaviors from positive to negative reinforcement (Koob, 2003). In brief, the individual becomes tolerant to the initial rewarding, positively reinforcing effects of alcohol, while gradually becoming sensitized to the non-rewarding, negatively reinforcing aspects of drinking, including withdrawal symptoms and preoccupation with alcohol. As the influence of the non-rewarding, negatively reinforcing aspects of alcohol use increases, the balance between the two types of reinforcement is disrupted. Drinking then becomes driven by the motivation to prevent or alleviate negative affective consequences and/or physical withdrawal symptoms experienced upon alcohol intake cessation, thus feeding 'the dark side' of addiction (Koob, 2015).

A similar disruption of the typically cautionary function of acute pain is found in patients with chronic pain. Approximately 11% of adults in the USA suffer from daily chronic pain (Nahin, 2015), which is defined as pain that persists for at least 3–6 months (Treede *et al*., 2015). In healthy individuals, acute pain serves as a salient (meaning important and notable) stimulus that activates sensing, integrating and stabilizing physiological mechanisms to allow the body to respond through homeostatic and allostatic modifications. The power of this ability to re-establish nociceptive balance is illustrated by human and animal studies showing that only a small proportion of individuals who have sustained an injury develop chronic pain (De Felice *et al*., 2011; Staud, 2012; Heinricher, 2016). Conversely, prolonged use of analgesic drugs—including but not limited to opioids—leads to potentiated pain, as observed by the occurrence of medication-overuse headache and opioid-induced hyperalgesia upon extended use (Compton *et al*., 2001; Diener *et al*., 2016; Roeckel *et al*., 2016). It is now therefore thought that aberrant processing observed in chronic pain states involves both 'sensitization' of pain-transmission systems and dysfunction in descending modulatory mechanisms, including those activated by analgesic drugs (Woolf, 2011; Borsook *et al*., 2013; Bannister and Dickenson, 2016; Arendt-Nielsen *et al*., 2018).

These parallels in the disruption of balance during the progression to AUD from otherwise non-problematic alcohol use or to chronic pain from acute pain suggest potential common underlying mechanisms and an intersection of relevant nuclei and neural circuits. Possible areas of overlapping circuitry and areas of activation are depicted in Fig. 1 and discussed below.

NEURONAL ACTIVATION AND CIRCUITRY IN BOTH AUD AND PAIN

Neuronal activation and circuitry implicated in AUD

The escalation of non-problematic alcohol use to AUD can be described in three repeating yet escalating stages: (a) binge/intoxication, (b) withdrawal/negative affect and (c) preoccupation and/or anticipation (or craving) (Koob and Volkow, 2010). Brain regions associated with each of these stages have been identified through brain mapping studies of immediate early gene (IEG) expression at various stages of alcohol exposure (for a full review, see Vilpoux *et al*. (2009)).

The first stage, binge/intoxication, is best modeled by voluntary alcohol self-administration. Mapping of the IEG c-Fos following voluntary alcohol self-administration has demonstrated inhibition of hippocampus (Hipp) and activation of the centrally projecting Edinger–Westphal nucleus (EWcp) following acute alcohol exposure. The IEG responses in these two regions appear to be specific to the actions of alcohol rather than general novelty, stress, or any other non-specific aspects of the behavioral paradigm (Ryabinin, 1998; Ryabinin and Giardino, 2017). In some (but not all) voluntary alcohol drinking paradigms, the central nucleus of amygdala (CeA) and nucleus accumbens (NAC) have also been reported to be activated (Bachtell *et al*., 1999; Anacker *et al*., 2011). The EWcp and CeA have been the only two regions exhibiting c-Fos induction following alcohol exposure in anesthetized animals (Smith *et al*., 2016b) and thus are linked to alcohol exposure *per se* rather than to alcohol cues or perception of alcohol intoxication. Additional nuclei are activated during acute, experimenter-administered alcohol exposure and may also relate to intoxication. These include the ventral tegmental area (VTA), prefrontal cortex (PFC), dorsal striatum (DS), globus pallidus, bed nucleus of the stria terminalis (BNST) and subregions of thalamus (Thal) (Hitzemann and Hitzemann, 1997; Ryabinin *et al*., 1997; Thiele *et al*., 1997; Bachtell and Ryabinin, 2001). Although it is acknowledged that the non-voluntary exposure paradigms may engage circuits not normally activated during voluntary consumption of alcohol, it has been hypothesized that the regions outlined above comprise an interconnected network activation that is recruited in the first stage of alcohol use, underlying the first stage of addiction (Koob and Volkow, 2010) (Fig. 1A).

The second stage of escalating alcohol use is withdrawal and negative affect in the absence of alcohol. Again considering IEG as

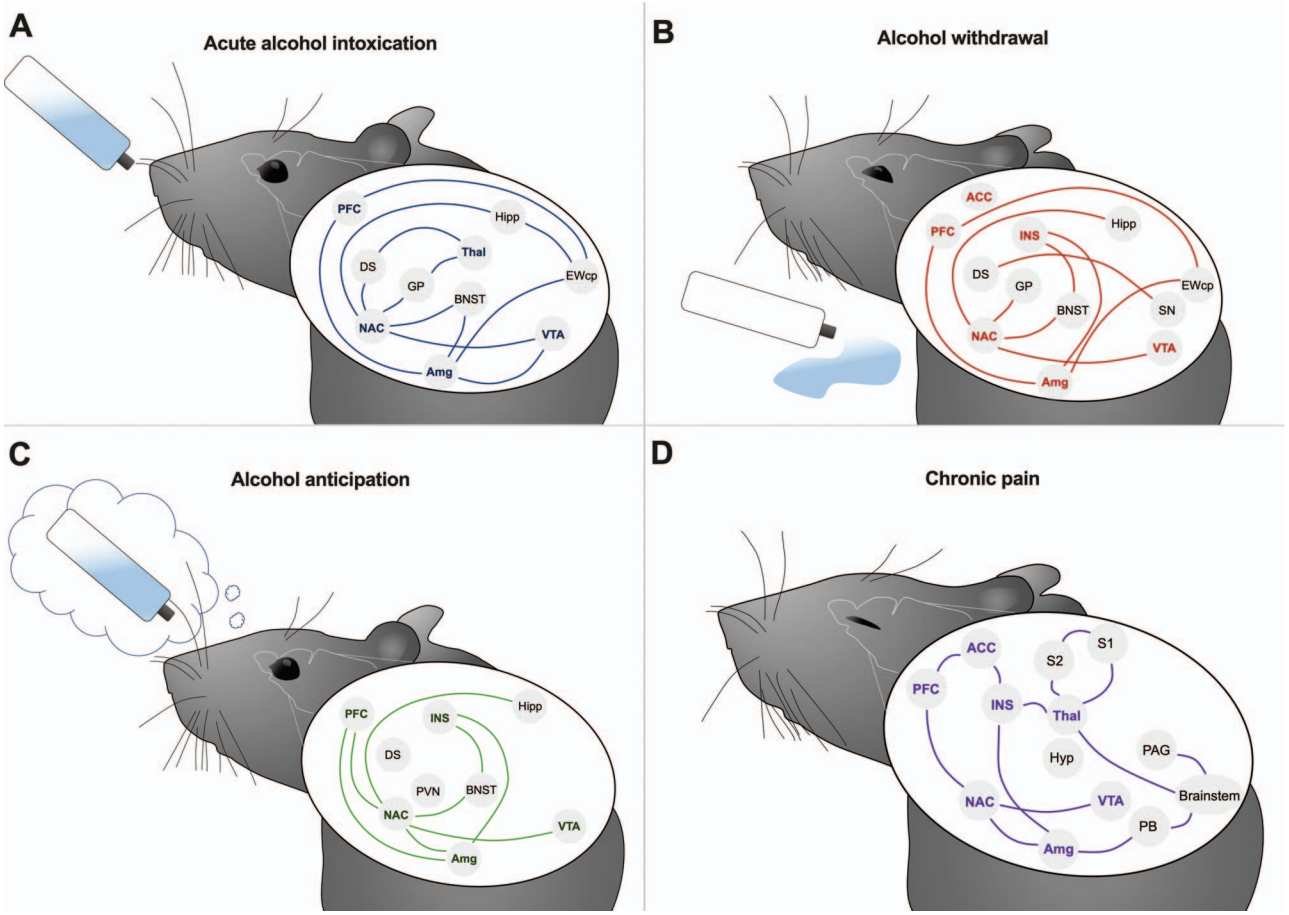

Fig. 1. Neurocircuitry activated during alcohol use or pain. Reward, emotional and nociceptive systems contribute to alcohol intoxication (**A**), alcohol withdrawal (**B**), alcohol anticipation (**C**) and pain (**D**). Anterior cingulate cortex (ACC), amygdala (Amg), bed nucleus of the stria terminalis (BNST), centrally projecting Edinger-Westphal nucleus (EWcp), dorsal striatum (DS), globus pallidus (GP), hippocampus (Hipp), hypothalamus (Hyp), insula (INS), nucleus accumbens (NAC), periaqueductal gray (PAG), parabrachial nucleus (PB), prefrontal cortex (PFC), thalamus (Thal), substantia nigra (SN), primary somatosensory cortex (S1), secondary somatosensory cortex (S2). Bold names indicate overlap between nuclei recruited in both alcohol and pain systems.

indicators of relevant brain regions, the VTA, Hipp, lateral septum, insula (INS), anterior cingulate cortex (ACC), subregions of the amygdala (Amg), EWcp, substantia nigra (SN), globus pallidus, medial habenula, locus coeruleus, cerebellum and dorsomedial hypothalamus (Hyp) are hypothesized to form a network associated with withdrawal and negative affect that drives further alcohol intake via negative reinforcement (Fig. 1B) (Putzke *et al*., 1996; Kozell *et al*., 2005; Chen *et al*., 2009; Smith *et al*., 2017). In this stage, the VTA, NAC, habenula and extended Amg are assumed to generate a negative emotional state and stress responses that coincide with an elevated reward threshold, referred to as anhedonia (Garavan *et al*., 2000). Increased activity of the hypothalamic–pituitary–adrenal axis [including modulations in the corticotropin-released factor (CRF) system], as well as increased dynorphin release (an endogenous kappa-opioid agonist), is observed during this period, resulting in an anxiogenic state (Koob, 2008).

The third stage of AUD is preoccupation, or anticipation. IEG mapping studies have confirmed the PFC, NAC, subregions of Amg and Hipp, BNST, the paraventricular nucleus of Hyp and VTA as regions activated upon exposure to cues predicting alcohol self-administration (Harlan and Garcia, 1998; Zhao *et al*., 2006; Hill *et al*., 2007; Vilpoux *et al*., 2009). Human and rodent studies investigating either cue- or stress-induced reinstatement further implicate three pathways in this response: (a) glutamatergic projections from the PFC, basolateral Amg and Hipp onto the NAC; (b) dopaminergic modulation in the basolateral Amg and DS and (c) increased CRF system activity in the extended Amg and VTA (Valdez *et al*., 2002; De Witte *et al*., 2005; Kalivas, 2009) (Fig. 1C).

Circuits implicated in chronic pain

Having both sensory-discriminative and affective dimensions, acute pain serves as a useful warning of impending or actual tissue damage, and its affective aspect motivates escape from the damaging stimulus and supports learning to avoid such stimuli in the future. This adaptive value is not evident in chronic pain. Here, pain is evoked by innocuous sensory inputs that are neither damaging nor normally painful. This latter observation is at least in part due to 'sensitization' of pain-processing circuitry, including primary afferent nociceptors, central pain transmission pathways and alterations in descending modulatory systems (Ji and Woolf, 2001; Heinricher, 2016; Thompson and Neugebauer, 2018). The neural circuitry associated with chronic pain has been assessed not using IEG mapping (because expression of these genes tends to habituate with chronic stimulation (Melia *et al*., 1994)) but instead by a combination of electrophysiological, pharmacological, behavioral, anatomical and,

more recently, optogenetic and chemogenetic approaches in a range of animal models. This large body of evidence points to somatosensory pathways with ascending pathways relaying information to reticular formation in the brainstem, Hyp, Amg and cortex (including somatosensory cortex, INS and ACC). These ascending signals engage structures important in motivation and emotion, including mesolimbic dopaminergic systems implicated in salience encoding (Berridge, 2018). Given the increased salience of pain-related information in chronic pain states (Borsook *et al*., 2013; Kucyi and Davis, 2015), it should not be surprising that alterations in neuronal activation following painful stimuli and alterations in functional connectivity between mesolimbic structures and a number of cortical regions have been observed in functional imaging studies of patients with chronic pain (Apkarian *et al*., 2005; Baliki and Apkarian, 2015). Increased functional connectivity between the NAC and the PFC predicts pain persistence in patients with chronic lower back pain (Baliki *et al*., 2012), and painful stimuli evoked increased activity in the PFC and decreased activity in the ACC, primary somatosensory cortex (S1), secondary somatosensory cortex (S2), insular cortex and Thal in patients with clinical pain conditions (Apkarian *et al*., 2005). Interestingly, in individuals with acute low back pain, activation was concentrated in sensory regions such as the Thal and INS, whereas in patients with chronic back pain, it was focused in emotion-related circuitry (medial PFC, Amg) (Baliki *et al*., 2006; Hashmi *et al*., 2013), an observation consistent with an increasing contribution of motivational circuits in chronic pain. The circuitry recruited in both the sensory and affective responses to pain is illustrated in Fig. 1D.

Intersection of circuits implicated in AUD and pain

The idea that the comorbidity between AUD and chronic pain could be the result of a network overlap between regions engaged by excessive alcohol use and pain has been proposed previously (Egli *et al*., 2012). Further analysis of the neuronal circuits engaged during chronic pain (Fig. 1D) suggests a resemblance to those involved in the withdrawal and preoccupation/anticipation stages of AUD (Fig. 1B and C), reflecting the centrality of incentive salience in both behavioral states and the importance of the emotional components and a potential rationale for the comorbidity of AUD and chronic pain.

MOLECULAR RATIONALE FOR INTERSECTION BETWEEN AUD AND CHRONIC PAIN

The intersection between pain and alcohol in the central nervous system is also apparent due to an overlap in engaged neuronal modulators. Earlier reviews on the interaction between alcohol and pain focused on this overlap (Egli *et al*., 2012; Apkarian *et al*., 2013; Witkiewitz and Vowles, 2018). However, with the progress in understanding of these pathways, an update is in order. Here, we emphasize four major molecular mechanisms implicated in both pain and AUD: glutamate and gamma-Aminobutyric acid (GABA), opioids, CRF/urocortins (Ucns) and protein kinase C-epsilon (PKCε).

Glutamate and GABA

Alcohol inhibits the activity of ionotropic glutamate receptors acutely, consequently decreasing excitatory neurotransmission (Lovinger and Roberto, 2013). Alcohol also acts as a potential positive allosteric modulator of the $GABA_A$ receptor, thereby increasing GABA-mediated inhibition throughout the central nervous system (Korpi, 1994; Davies, 2003; Olsen *et al*., 2007; Lovinger and Roberto, 2013). This increased inhibitory effect of GABA is associated with sedation, inhibition of memory formation, altered reward and hypoalgesia following acute alcohol intake (Lobo and Harris, 2008). However, chronic alcohol use is associated with a paradoxical decrease in inhibitory GABA transmission and increase in excitatory glutamatergic transmission, presumably representing a compensatory response to the enhanced inhibitory tone from continued alcohol consumption (Wang *et al*., 2007; Holmes *et al*., 2013; Cheng *et al*., 2017). This disruption in the balance between excitatory and inhibitory transmission is thought to play a role in alcohol tolerance and dependence (defined as adaptive physiological changes where cessation of drug causes withdrawal symptoms) and is accentuated in alcohol withdrawal when the modulatory influence of alcohol on GABA receptors is no longer present (Madamba *et al*., 1996; Berton *et al*., 1998).

Altered levels of centrally acting glutamate and GABA are also observed in chronic pain conditions. Increased glutamate and decreased GABA levels have been observed in the anterior INS, ACC and Thal in diabetic neuropathy patients (Petrou *et al*., 2012), and increased glutamate has also been seen in the INS in patients with fibromyalgia (Kaplan *et al*., 2019). These observed changes in decreased endogenous GABAergic activity but increased glutamatergic activity in both chronic pain and AUD suggest that modifying the balance between these neurotransmitter levels may reinstate proper pain modulation while decreasing alcohol withdrawal-induced neuronal hyperexcitability. However, studies investigating this claim pharmacologically are limited (Enna and McCarson, 2006; Carter *et al*., 2014), likely because of the well-known sedative effects of GABA receptor agonism.

Opioids

Opioid alkaloids have long been recognized as potent analgesics, and opioids continue to be the mainstay for treatment of severe acute pain. Endogenous opioids contribute to the rewarding properties of natural reinforcers through their primary actions in the VTA, resulting in disinhibition leading to increased dopamine release onto the NAC (Fields and Margolis, 2015). It should therefore not be surprising that endogenous opioids play a role in the rewarding aspects of other drugs of abuse, including alcohol, and that exogenous opioids themselves come with significant abuse potential.

The opioid receptor family contains three major subtypes—mu (MOR), delta (DOR) and kappa (KOR) opioid receptors. Activity at MOR is required for morphine analgesia, as demonstrated by lack of this analgesia in MOR knockout (KO) animals (Loh *et al*., 1998). While MOR agonism indeed results in rapid analgesia, tolerance also develops quickly (Ho *et al*., 1973; Chavkin and Goldstein, 1984), thus leaving MOR-targeted therapeutics a poor choice for chronic pain conditions. Furthermore, direct administration of MOR agonists in reward-associated regions such as the NAC is associated with increased alcohol intake (Richard and Fields, 2016). Conversely, MOR-KO mice do not readily self-administer alcohol (Roberts *et al*., 2000). Therefore, while MOR agonists provide acute pain relief, they may also increase the risk of AUD, rendering MOR-targeted therapeutics a hazardous choice for those with comorbid chronic pain and AUD (further discussed under '*AUD and opioid use disorder comorbidity*').

In contrast to the abuse liability concerns of MOR, DOR agonists do not produce potent analgesia in acute pain states, and activation

of DOR is not commonly associated with reward (Do Carmo *et al*., 2009; Pradhan *et al*., 2014). However, DOR agonists can produce analgesia in persistent pain states (Pradhan *et al*., 2011; Vicente–Sanchez *et al*., 2016; Abdallah and Gendron, 2018). Exogenous DOR agonists can also differentially affect voluntary alcohol intake and alcohol reward (van Rijn *et al*., 2012a; Chiang *et al*., 2016) and decrease alcohol withdrawal-induced anxiety-like behaviors in mice (van Rijn *et al*., 2012b). Moreover, DOR-KO mice display greater anxiety-like behavior, increased alcohol intake (Roberts *et al*., 2001) and increased hyperalgesia following inflammation (Gaveriaux-Ruff *et al*., 2008), suggesting that endogenous DOR activity is protective in both alcohol-related behaviors and chronic pain.

While MOR and DOR have roles in both pain relief and reward, KORs in the mesolimbic reward system contribute to the aversive affective components of drug withdrawal and chronic pain (Walker *et al*., 2012; Karkhanis *et al*., 2017). Increases in the endogenous KOR agonist dynorphin lead to decreased dopamine release in regions such as the NAC, resulting in dysphoria and stress (Goldstein *et al*., 1979; Anderson and Becker, 2017). Taken as a whole, these finding might suggest that KOR antagonists would be beneficial in treating negative affect in both alcohol withdrawal and chronic pain (Walker *et al*., 2012; Liu *et al*., 2019; Massaly *et al*., 2019). However, KOR antagonists have thus far largely failed in clinical trials for the treatment of drug dependence or depression (Rorick-Kehn *et al*., 2014; Buda *et al*., 2015), although investigations are ongoing.

Corticotropin-releasing factor and urocortins

Both injury and AUD engage the CRF system (Vale *et al*., 1981; Heilig and Koob, 2007). The components of this system in mammals include four ligands (CRF, Ucn1, Ucn2 and Ucn3), two main receptors (CRFR1 and CRFR2) and the CRF-binding protein (Dedic *et al*., 2018). CRF primarily targets CRFR1, Ucn2 and Ucn3 target CRFR2, while Ucn1 targets both CRFR1 and CRFR2 (Pal *et al*., 2010). Genetic deletion or pharmacological blockade of CRFR1 can interfere with total fluid consumption, suggesting non-specific regulation of motivated behavior (Giardino and Ryabinin, 2013; Giardino *et al*., 2017). In contrast, genetic deletion of Ucn1 or short hairpin RNA interference with Ucn1 expression selectively suppresses the escalation of alcohol drinking to excessive drinking in mice (Giardino *et al*., 2017). Enhanced alcohol consumption in models of severe physiological alcohol dependence selectively depends on CRF acting on CRFR1 receptors (Chu *et al*., 2007; Heilig and Koob, 2007; Roberto *et al*., 2010).

There is also evidence that the CRF system contributes to interactions between stress and both pain and AUD. The interactions between stress and pain are complex, with mild stress inducing hyperalgesia and intense stress producing analgesia (Amit and Galina, 1988; Martenson *et al*., 2009). CRFR1 antagonists interfere with anxiety-like behaviors as well as hyperalgesia in rodents subjected to a chronic inflammatory pain state, and there is emerging evidence that this effect is because of interference with CRFR1-mediated sensitization of nociresponsive neurons in the CeA (Ji *et al*., 2007; Liang *et al*., 2007; Fu and Neugebauer, 2008). CRFR1 antagonists can also attenuate hyperalgesia associated with alcohol withdrawal, presumably a form of stress-induced hyperalgesia (Edwards *et al*., 2012). Stress can also induce alcohol-seeking in rodents with established alcohol dependence. This behavior, which can be considered a model of 'relapse' in abstinent individuals with AUD, is reduced by CRFR1 antagonism (Le *et al*., 2000; Liu and Weiss, 2002). There is thus substantial evidence that peptides acting on the CRFR1 receptor (CRF and Ucn1) could play a role in the chronic pain-AUD comorbidity. Nevertheless, CRFR1 antagonists failed to decrease subjective alcohol-induced cue and stressor craving in human subjects (Kwako *et al*., 2015; Schwandt *et al*., 2016). More studies are required to evaluate whether this failure may reflect additional factors brought into play in human populations with AUD.

Protein kinase C-epsilon

Changes in PKCε activity correspond with changes in activity throughout the central nervous system and associated behaviors, including alcohol consumption and pain. For example, inhibition of PKCε kinase activity by small molecule inhibitors decreases alcohol intake and preference in C57Bl/6 mice with no changes in ethanol clearance (Blasio *et al*., 2018). These effects are in line with genetic studies reporting that PKCε KO mice consume less alcohol than wild-type mice (Hodge *et al*., 1999) and display aversion to alcohol (Newton and Messing, 2007). PKC inhibitors also decrease alcohol neuropathy-induced hyperalgesia in rats (Dina *et al*., 2000). Conversely, PKC activators such as 12-myristate 13-acetate increase nociception upon intraplantar injection in mice (Ferreira *et al*., 2005). As inhibitors of isozymes such as PKCε decrease alcohol-related behaviors and additionally decrease pain responses, inhibitors of PKCε may be central point of molecular convergence between AUD and chronic pain signal transduction, consequently providing a potential therapeutic option for treating comorbid pain and AUDs.

ALCOHOL USE AND POTENTIATED PAIN

Epidemiological studies indicate that AUD is associated with an increased prevalence of chronic pain. In a 2007 study assessing pain persistence in detoxified patients, 73% of patients who identified alcohol as their drug of choice (as compared with opioids or cocaine) reported moderate-to-severe pain in the previous month and 24% reported pain throughout the duration of the 2-year study period (Larson *et al*., 2007). Another study noted that ~30% of employed, alcoholic patients attending a drug and alcohol treatment program reported severe chronic pain (Sheu *et al*., 2008). Problem drinking is also associated with increased prevalence of moderate-to-severe pain among older adults (Brennan *et al*., 2005). Increased complaints of pain in AUD are likely because of multiple factors occurring at distinct time scales. These include not only acutely enhanced pain associated with acute alcohol withdrawal and AUD but also chronic pain due to peripheral neuropathic effects of alcohol (Monforte *et al*., 1995) (Fig. 2), and perhaps, an increased susceptibility for chronic pain as a result of altered brain circuits associated with AUD progression (as suggested by the overlap in neuronal circuitry in Fig. 1).

Acute hyperalgesia and allodynia associated with withdrawal from alcohol

Cessation of occasional binge alcohol consumption is followed by a hangover (Slutske *et al*., 2003; Verster, 2008; Penning *et al*., 2012). During the development of AUD, hangovers increase in frequency and severity. Despite common knowledge linking hangovers with increased pain, surprisingly few studies have investigated the hyperalgesic effect of alcohol withdrawal in humans. In one experimental study, male patients with a history of alcohol dependence undergoing

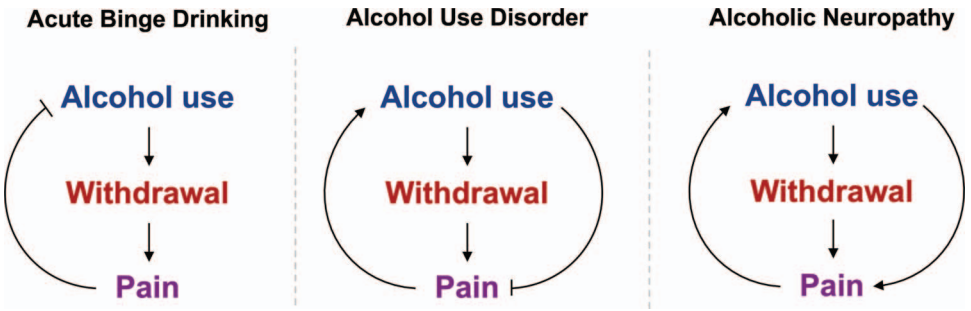

Fig. 2. Evolution of pain's influence on alcohol use during progression from binge drinking to AUD to alcoholic neuropathy. Following cessation of acute binge drinking, hangover causes pain during the acute withdrawal phase, which can increase time between drinking events. In AUD, cessation of alcohol use also causes pain; however, subjects may continue to drink alcohol to alleviate this withdrawal pain or other pain causes. When alcohol use is long-term and chronic, alcoholic neuropathy can develop, where alcohol use no longer provides analgesia and further alcohol intake can increase pain sensation.

alcohol withdrawal displayed reduced tolerance for noxious thermal stimuli (Jochum *et al*., 2010), with no change in thermal pain threshold. Potentiated pain during hangover is thus documented primarily by anecdote.

By contrast with limited data in humans, alcohol withdrawal-induced hyperalgesia (increased pain evoked by normally painful stimuli) and allodynia (decrease in threshold so that innocuous stimuli are perceived as painful) have been amply demonstrated in laboratory animals. Different models of alcohol exposure have been used to assess hyperalgesia during withdrawal (Table 1). Experimenter-controlled or no-choice procedures of alcohol administration have allowed researchers to control the amount of administered alcohol and have documented significant hyperalgesia during acute withdrawal. Early studies used liquid diet-based approaches to study alcohol-induced hyperalgesia in rats, where 4–10 days of no-choice exposure to a 6.5% ethanol liquid diet or 72-day exposure to escalating 2–5% ethanol liquid diet resulted in hyperalgesia upon withdrawal (Gatch and Lal, 1999; Dina *et al*., 2006; Gatch, 2006; Narita *et al*., 2007b). More recently, mechanical hyperalgesia in rats has also been reported after prolonged alcohol vapor exposure (Edwards *et al*., 2012; Avegno *et al*., 2018). Alcohol administered by oral gavage (2 or 3 g/kg over the course of 3 weeks) has been shown to induce mechanical allodynia 24 hours following last alcohol exposure in mice (Alongkronrusmee *et al*., 2016).

Despite the robust effects of experimenter-administered alcohol, these strategies provide less translation to human studies where subjects consume alcohol voluntarily. Comparison of alcohol withdrawal in mice after alcohol gavage vs. voluntary drinking (via a two-bottle choice procedure) for 3 weeks resulted in a more pronounced (and longer-lasting) mechanical allodynia in gavaged animals, suggesting either that the rate of alcohol administration or the interaction with stress induced by the mode of administration affects the development of allodynia (Alongkronrusmee *et al*., 2016). Nevertheless, it is reassuring that withdrawal-induced hyperalgesia has been observed in this and other rodent models of self-administration. Mechanical hyperalgesia was observable 24 hours following 4 days of alcohol exposure in a model of exposure using a drinking-in-the-dark protocol between water and 20% alcohol in mice (Bergeson *et al*., 2016). Additionally, alcohol-induced mechanical, thermal and chemical hyperalgesia has been observed in C57Bl/6J male mice at 24 hours of ethanol withdrawal after continuous access to 10% ethanol and water for 6 days (Smith *et al*., 2016a). Longer exposure strategies, such as 12 weeks of intermittent access to a two-bottle choice (water vs. 20% alcohol) resulted in very robust hyperalgesia, as assessed through thermal or mechanical hyperalgesia/allodynia, as well as other withdrawal symptoms including tail stiffness, decreased ambulation and lower-limb flexion. Mechanical hypersensitivity was evident for up to 7 days post-withdrawal (Fu *et al*., 2015). One caveat with prolonged exposures to alcohol is that this strategy might also give rise to peripheral neuropathy, also known as alcoholic neuropathy.

Alcoholic neuropathy

Following years of heavy drinking, AUD patients may be diagnosed with alcoholic neuropathy. Alcoholic neuropathy is estimated to affect 25–66% of AUD patients in the United States and is most common in frequent, heavy drinkers compared with episodic drinkers (Monforte *et al*., 1995). It is also more common in women than in men (Ammendola *et al*., 2000). Alcohol-induced neuropathy manifests as pain and abnormalities in sensory, motor and autonomic functions (Chopra and Tiwari, 2012), and these clinical features are associated with axonopathy and reduced nerve fiber density (Koike *et al*., 2001). The exact cause of alcoholic neuropathy is unknown, and no effective therapeutics are currently available. Patients are nevertheless counseled to decrease and/or cease further alcohol use to prevent disease progression.

One potential mechanism of alcohol-induced neuropathy is thiamine (vitamin B_1) deficiency, as ethanol decreases thiamine absorption in the intestine and thus depletes stores of thiamine and thiamine phosphorylation (Singleton and Martin, 2001). This decrease in cellular thiamine levels is proposed to disrupt carbohydrate metabolism, leading to increased oxidative stress or mitochondrial load, resulting in apoptosis or necrosis, respectively (Singleton and Martin, 2001). An additional suggested mechanism for alcoholic neuropathy is increased acetaldehyde accumulation as the result of ethanol metabolism, which can lead to enhanced cytokine production, potentiated oxidative stress and/or increased mitogen-activated protein (MAP) kinase or PKC signaling (Chopra and Tiwari, 2012). Microglial activation and hypertrophy have also been reported (Narita *et al*., 2007c). These observations raise the possibility that the axonopathy and functional changes with prolonged alcohol consumption reflect a neuroinflammatory insult. Consistent with this, rolipram, a selective phosphodiesterate-4 (PDE4) inhibitor that can reduce levels of proinflammatory cytokines, decreases mechanical allodynia in male ethanol-exposed rats (Pearse *et al*., 2004; Han *et al*., 2012).

In addition to neuroimmune mechanisms, alterations in glutamate receptor phosphorylation have been observed in alcoholic

Table 1. Reported rodent models assessing alcohol-induced hyperalgesia/allodynia

Rodent models of alcohol-induced hyperalgesia/allodynia

Model	Timeline	Species/strain/sex	Analgesic test performed	Reference
Self-administration				
Continuous access two-bottle choice (water vs. increasing concentrations of alcohol, 3–6–10%)	6 days of alcohol exposure/week Analgesic response measured 24 hours following alcohol removal	Mouse C57Bl/6J Male only	Mechanical (von Frey) Thermal (heat, tail-flick) Inflammatory (formalin)	Smith *et al.* (2016a)
Drinking-in-the-dark two-bottle choice (water vs. 10% alcohol)	3 weeks of alcohol exposure (4 hours/5 days a week) Analgesic response measured 1, 2, 4, 7 and 14 days following alcohol removal	Mouse C57Bl/6 Male only	Mechanical (von Frey)	Alongkronrusmee *et al.* (2016)
Drinking-in-the-dark (water vs. 20% alcohol)	4 days of alcohol exposure (4 hours/day) Analgesic responses measured 1, 5–11 days following alcohol removal	Mouse C57Bl/6 Male and female	Inflammatory (formalin) Mechanical (von Frey) Thermal (cold, acetone evaporation)	Bergeson *et al.* (2016)
Intermittent access, two-bottle choice (water vs. 20% alcohol)	12 weeks of alcohol exposure (24 hours/5 days a week) Analgesic responses measured after 4, 8 or 12 weeks of alcohol exposure	Rat Sprague-Dawley Male only	Mechanical (von Frey) Thermal (heat, radiant heat)	Fu *et al.* (2015)
No-choice self-administration				
Liquid diet containing ethanol (6.5%)	10 days of liquid diet exposure Analgesic response measured 3, 6, 12 and 36 hours following ethanol removal	Rat Long–Evans Male only	Thermal (heat, tail-flick)	Gatch, (2006), Gatch and Lal (1999)
Liquid diet containing ethanol (6.5%)	4 days of liquid diet, 3 days of standard chow ('4 days on/3 days off') for 5 weeks Analgesic response measured 3 days following alcohol removal	Rat Sprague-Dawley Male only	Mechanical (Randall–Selitto)	Dina *et al.* (2006)
Liquid diet containing ethanol (escalating, 2.5% to 5%)	72 days of alcohol exposure Analgesic response measured once every 5 days after 7 days following alcohol removal	Rat Fischer 344 Male	Mechanical (Randall–Selitto)	Narita *et al.* (2007b)
Experimenter-controlled				
Chronic intermittent alcohol vapor[a]	11–12 weeks of alcohol vapor (14 hours/day) Analgesic response measured during withdrawal period (8 hours after vapor off)	Rat Wistar Male only	Mechanical (von Frey)	Edwards *et al.* (2012)
Chronic intermittent alcohol vapor	4–9 weeks of alcohol vapor (14 hours/day) Analgesic response measured during withdrawal period (6–8 hours after vapor off), twice weekly	Rat Wistar Male only	Thermal (Hargreaves')	Avegno *et al.* (2018), Roltsch Hellard *et al.* (2017)
Oral gavage (2 or 3 g/kg ethanol)	3 weeks of alcohol exposure (5 consecutive days/week) Analgesic response measured 24 hours after final alcohol exposure	Mouse C57Bl/6 Male only	Mechanical (von Frey)	Alongkronrusmee *et al.* (2016)

Models described assessed acute withdrawal-induced hyperalgesia or allodynia. Does not include models of alcoholic neuropathy.
[a] Animals also exposed to two-bottle choice (10% ethanol vs. water) and ethanol operant self-administration (12 hours/session, 12 sessions) prior to vapor exposure.

neuropathy, and these may contribute to alcoholic neuropathy symptomatology (Bu *et al.*, 2015). Male Fischer 344 rats exposed to an ethanol-containing liquid diet for 70 days displayed mechanical allodynia that persisted for at least 14 weeks after alcohol was removed. There was a significant increase in phosphorylation of the Ser-13030 site of the N-methyl D-aspartate receptor subtype 2B (NR2B) subunit for the N-methyl D-aspartate (NMDA) receptor in the spinal cord of ethanol-fed mice compared with non-ethanol-fed controls (Narita *et al.*, 2007a). It is possible that this phosphorylation is the result of increased PKC activity, since increased phosphorylated-PKC immunoreactivity was observed in the spinal cord of rats fed ethanol chronically (Narita *et al.*, 2007b). These authors also reported dysfunction of MORs. Overall, a host of direct and indirect factors may contribute to the pathogenesis of alcoholic neuropathy and resulting hyperalgesia, although future studies are necessary to assess the causal role of each component.

PAIN GIVING RISE TO INCREASED ALCOHOL USE

As already noted, alcohol has long been used as an analgesic. Alcohol administration has been reported to increase pain tolerance, even at non-intoxicating doses (Woodrow and Eltherington, 1988; Horn-Hofmann *et al.*, 2015). Acute ethanol administration can also relieve hyperalgesia, as described, for example in a study investigating the effect of ethanol on capsaicin-induced hyperalgesia in human volunteers (Arout *et al.*, 2016). These effects of alcohol on acute and potentiated pain raise the possibility that hyperalgesia could drive consumption of alcohol. Consistent with this idea, many drinkers indicate that they consume alcohol to moderate pain (Brennan *et al.*, 2005; Riley and King, 2009).

Acute experimental pain can motivate alcohol consumption. Moderate-to-heavy drinkers report a greater urge and intention to drink when subjected to an experimental hyperalgesia protocol (Moskal *et al.*, 2018). Importantly, however, this study was conducted in individuals exposed to acute pain (apparently otherwise pain-free), and the results do not necessarily reflect alcohol's effects on chronic pain. A 2015 UK study found a strong correlation between alcohol consumption and reported level of chronic widespread pain. Participants with chronic pain were less likely to report pain symptoms as debilitating if they also reported consuming alcohol regularly (Macfarlane and Beasley, 2015). Similarly, participants who consumed elevated levels of alcohol were also less likely to report chronic widespread pain symptoms in general. In patients with fibromyalgia, low and moderate alcohol consumption was associated with higher quality of life and lower symptom reporting compared with those who did not consume alcohol (Kim *et al.*, 2013). However, a positive relationship between chronic pain and alcohol intake is not a uniform finding. Adolescents with chronic pain were less likely to use alcohol compared with adolescents without chronic pain (Law *et al.*, 2015). Swedish adults diagnosed with long-term musculoskeletal pain reported a lower level of alcohol intake compared with an age-matched control group. Patients with chronic pain drank less often, in small quantities, and became intoxicated less frequently than those without chronic pain (Thelin Bronner *et al.*, 2012). Finally, although alcohol use was associated with a decrease in the frequency of reported pain in individuals with orofacial pain or arthritis, there was no correlation with reduced intensity or chronicity of pain (Riley and King, 2009). These disparate findings may reflect that while alcohol consumption is acutely analgesic, its efficacy, like that of most known analgesic drugs, diminishes with chronic use (Gatch and Lal, 1999; Thompson *et al.*, 2017). A complex interplay between analgesia, pain and other physiological, psychological and social sequelae of alcohol consumption is likely at work in individuals with chronic pain and AUD.

Pain relief is rewarding and produces negative reinforcement in rodents, as shown by increased conditioned place preference to contexts associated lidocaine administration in rats with incisional injury-induced pain (Navratilova *et al.*, 2012). Thus, it is conceivable that rodents consume alcohol for analgesia as a negative reinforcer. However, two questions must be asked regarding alcohol's analgesic effects: (a) does pain increase alcohol intake? and (b) is potential increased alcohol intake the result of alcohol's analgesic effects?

A summary of known preclinical investigations addressing these questions is provided in Table 2. With regard to the first question, in a model for osteoarthritis in C57Bl/6 mice, mice in the osteoarthritis group consumed more alcohol and preferred 20% ethanol in a two-bottle choice protocol compared with control mice (Butler *et al.*, 2017). Furthermore, severity of the osteoarthritis correlated with alcohol intake, thus suggesting that the analgesic effects of alcohol led to the increased alcohol consumption. In a different model, male C57Bl/6 mice subjected to localized inflammation of the hind paw exhibited increased alcohol intake in a two-bottle choice (20% alcohol vs. water), continuous access paradigm compared with controls, further supporting the idea that persistent pain increases alcohol intake (Yu *et al.*, 2018). However, it is worth noting that female mice in the same study showed no increase in alcohol consumption in persistent inflammation.

The two studies described above demonstrate that rodents, or at least male rodents, in persistent pain states increase alcohol intake. However, these studies did not determine whether the observed increase in alcohol consumption actually produced antinociception. CD1 mice subjected to a peripheral nerve injury consumed more ethanol in a drinking-in-the-dark procedure compared with sham-operated mice, yet cold hyperalgesia and depressive behaviors were not altered by ethanol consumption (Gonzalez-Sepulveda *et al.*, 2016). Smith and colleagues saw no increase in mechanical withdrawal threshold in mice with persistent inflammation that were given access to alcohol in a two-bottle choice procedure (Smith *et al.*, 2015). The lack of change in thermal and mechanical responding in these studies may be explained by low blood ethanol plasma levels, which may have been inadequate to produce detectable analgesia (Gatch, 2009). Nevertheless, alcohol intake did reverse ethanol withdrawal-induced hyperalgesia, with 4-hour access to 10% alcohol reversing mechanical hypersensitivity induced by withdrawal from a two-bottle choice procedure (Smith *et al.*, 2016a).

Overall, current work in animal models suggests that rodents will consume more alcohol when in pain and that alcohol consumption during pain can result in analgesia, although these findings are not consistent across studies. However, whether or not this increased alcohol intake is motivated by the desire to obtain analgesia or provide potential affective relief has not yet been decisively demonstrated. For affect, an important caveat is that anxiety- and depression-related behaviors typically do not appear until 4–8 weeks following neuropathic pain induction in mice (Yalcin *et al.*, 2011). This delayed appearance suggests that any motivation to consume alcohol following pain induction to alleviate pain-related changes in affect may not be apparent until at least 2–3 months following pain inducement.

Table 2. Preclinical reports of changes in drinking in response to pain

Model	Timeline	Species/strain/sex	Alcohol intake procedure	Changes in alcohol intake	Reference
Osteoarthritis	Alcohol consumption was assessed 13 weeks after surgical destabilization of the medial meniscus for 24 days	Mice C57Bl/6 Male only	Two-bottle choice (water vs. gradual increase in 2.5–20% alcohol), continuous access	Osteoarthritis increased alcohol intake and preference at 20% alcohol; severity of osteoarthritis correlated with alcohol intake	Butler *et al.* (2017)
Hind paw inflammation	Alcohol consumption was assessed 3 days after injection of complete Freund's adjuvant into the hind paw; consumption was monitored for 3 weeks	Mice C57Bl/6 Male and female	Two-bottle choice (water vs. 20% alcohol), continuous access	Increased alcohol intake in males, no change in alcohol intake in females	Yu *et al.* (2018)
Peripheral nerve injury	Alcohol consumption was assessed 33 days after partial sciatic nerve ligation for 10 days	Mice CD1 Male only	Single bottle access (20% alcohol), limited access (3 hours) 3 hours into dark/active cycle	Increased alcohol intake	Gonzalez-Sepulveda *et al.* (2016)

Models described assessed how pain influences voluntary alcohol intake.

ADDITIONAL CONSIDERATIONS

As the above discussion makes apparent, there are strong, bidirectional links between alcohol consumption and chronic pain, and progress has been made in understanding of mechanisms contributing to various aspects of these links (for example better understanding of the relevant neural circuits and molecular mechanisms). Nonetheless, many questions remain, including the influence of sex, social and environmental factors, how pain alters the efficacy of treatments for AUD and whether alcohol and opioid use disorders are related.

Sex as a biological variable

Throughout this review, the sex of the subjects assessed in each study has been specified to emphasize sex as a potential biological variable. Indeed, sex differences in both pain- and AUD-related behaviors are observed in both human subjects and rodents (Wiesenfeld-Hallin, 2005; Agabio *et al.*, 2017), where both biological and psychosocial mechanisms presumably contribute to these assessed sex differences (Ceylan-Isik *et al.*, 2010; Mogil, 2012; Bartley and Fillingim, 2013; Foster *et al.*, 2014).

For AUD, men have been historically more likely to be diagnosed with AUD (Helzer and Pryzbeck, 1988). However, this gender gap has recently decreased (Foster *et al.*, 2014; Erol and Karpyak, 2015; Agabio *et al.*, 2017). While women are more likely to seek treatment for AUD, both sexes are vulnerable to relapse. Men most commonly relapse because of social pressure, while women relapse because of negative affect (Zywiak *et al.*, 2006), and interestingly women exhibit fewer symptoms of withdrawal (Deshmukh *et al.*, 2003). Sex differences are commonly observed in preclinical research as well. Female rodents voluntarily consume more alcohol than males in both social and isolated housing (Li and Lumeng, 1984; Middaugh and Kelley, 1999; Yoneyama *et al.*, 2008). Notably, no effect of estrous cycle has been observed regardless of strain or drinking paradigm (Priddy *et al.*, 2017). Further investigations are necessary to see if the sex-related differences in withdrawal, negative affect and social support/pressure noted in humans are maintained across species.

As for pain, sex differences in pain threshold and sensitivity remain inadequately understood (Fillingim *et al.*, 2009; Racine *et al.*, 2012a; Bartley and Fillingim, 2013), although it is clear that many of chronic pain conditions (irritable bowel syndrome, fibromyalgia, migraine) are more prevalent in women than in men (Yunus, 2002; Stewart *et al.*, 2008). A variety of biological factors likely contribute to these differences in chronic pain prevalence, including differences in opioid receptor expression, gonadal hormone levels or neuroimmune responses (Bartok and Craft, 1997; Zubieta *et al.*, 2002; Cepeda and Carr, 2003; Loyd *et al.*, 2008; Sorge *et al.*, 2015; Rosen *et al.*, 2017; Sorge and Totsch, 2017). Differences in adaptive vs. innate immune responses observed in rodents in response to pain may explain the increased prevalence of autoimmune and inflammatory chronic pain conditions diagnosed in women compared with men (Mogil, 2012; Sorge *et al.*, 2015; White and Robinson, 2015; Sorge and Totsch, 2017). Further, some of the key psychosocial factors identified above for AUD (negative affect, social environment) may also influence how individuals report and cope with chronic pain (Keogh and Herdenfeldt, 2002; Racine *et al.*, 2012b; El-Shormilisy *et al.*, 2015). One study found that males are more capable of focusing on the sensory-discriminative aspects of pain, while women are more likely to concentrate on the affective dimension (Keogh and Herdenfeldt, 2002). Efforts are ongoing in both animals and humans to better understand how chronic pain expression and coping differs between the sexes and how this relates to treatment outcomes.

Transfer of pain by signals or communication

In addition to alcohol withdrawal causing pain in the individual, the social transfer of pain to 'bystander' animal has been described following alcohol withdrawal, opiate withdrawal or inflammatory pain in rodents housed in the same room (Smith *et al.*, 2016a; Walcott *et al.*, 2018). This effect appears to be mediated by olfactory signals in mice, although empathetic pain processing has been reported in humans in response to visual cues (Lamm *et al.*, 2011; Gu *et al.*, 2012). Furthermore, context-dependent pain hypersensitivity has

been observed in both male mice and humans (Martin *et al*., 2019). This implies that the potential effect of empathetic and/or context-dependent pain modulation should be considered in experimental and observational studies of pain in both animals and humans.

Influence of pain on alcohol treatment efficacy

Perceived pain can influence the efficacy of alcohol treatment outcomes. An association between pain and heavy drinking lapses during or after AUD treatment was observed even after controlling for other relapse factors, such as temptation, dependence severity and psychiatric distress (Witkiewitz *et al*., 2015; Jakubczyk *et al*., 2016). Similarly, alcohol consumption can influence post-surgical pain outcome. For example, 4 weeks of alcohol exposure prolonged post-surgical pain in C57Bl/6 mice (Liu *et al*., 2018), and patients with a history of AUD reported greater severity of pain 3 months after traumatic injury than did those without AUD (Holmes *et al*., 2010). These studies highlight the complexity of managing pain in individuals with AUD and addressing AUD in individuals with chronic pain.

AUD and opioid use disorder comorbidity

In the past few decades, abuse of both prescription and illicit opioids has increased explosively in the USA. This has resulted in increased opioid-related deaths, with ∼60% of drug overdose deaths involving opioids in the USA in 2014 (Rudd *et al*., 2016). Alcohol is consistently a contributing factor to many opioid overdose deaths as both alcohol and opiates act as central nervous system depressants, thus increasing the risk of respiratory depression (White and Irvine, 1999). A 2013 study found that ∼23% of adult patients diagnosed with opioid use disorder were also diagnosed with AUD, and the vast majority of these patients also had been diagnosed with a chronic pain condition (Hser *et al*., 2017), suggesting that chronic pain may be an important 'third variable' in the co-abuse of opioids and alcohol (Witkiewitz and Vowles, 2018). Because of the comorbidity of opioid use disorder and the depressant effects of both alcohol and opiates, it is conceivable that those recovering from opioid use disorder with chronic pain may consume alcohol as a means of pain management. However, little is known on the rates of use of alcohol as a substitution therapy, as no studies have formally investigated this following treatment for opioid use disorder. Moreover, opioid use disorder studies frequently exclude individuals with AUD because of the overlapping use of naltrexone for both opioid use disorder and AUD management (Witkiewitz and Vowles, 2018).

CONCLUSIONS

It is clear from preclinical and clinical investigations that alcohol use can lead to enhanced pain either acutely (during alcohol withdrawal) or chronically (via alcoholic neuropathy). Animal models of these effects are improving in sophistication, and progress in deciphering underlying neurocircuitry and neurochemical mechanisms underlying AUD-related hyperalgesia has been made. Nevertheless, this bidirectional relationship between alcohol and pain remains poorly understood. Furthermore, while pain has been demonstrated to increase alcohol intake, the motivation behind increased alcohol intake in those with chronic pain requires deeper analysis, as it could be contributed to either alcohol's analgesic effects or affective consequences (Koob, 2003; Egli *et al*., 2012). As a significant overlap in affective responding between chronic pain and alcohol withdrawal and preoccupation is noted (Paulus *et al*., 2017), studies investigating salience processing and emotional factors in comorbid subjects are warranted. Further studies are required to investigate these overarching questions and to interrogate developed models to help decipher the intricate relationship between pain and alcohol use.

CONFLICT OF INTEREST STATEMENT

None declared.

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