DR. SCOTT EDWARDS (Orcid ID : 0000-0002-0865-7758)

DR. KATIE WITKIEWITZ (Orcid ID : 0000-0002-1086-3067)

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Corresponding author mail id: sedwa5@lsuhsc.edu

Alcohol and Pain: A Translational Review of Preclinical and Clinical Findings to Inform Future Treatment Strategies

Scott Edwards*[1], Leandro F. Vendruscolo[2], Nicholas W. Gilpin[1], Marcin Wojnar[3,4], and Katie Witkiewitz[5]

Affiliations

[1] Department of Physiology and Comprehensive Alcohol-HIV/AIDS Research Center, LSU Health Sciences Center, New Orleans, LA 70112

[2] National Institute on Drug Abuse (NIDA), Intramural Research Program (IRP), Baltimore, MD 21224

[3] Department of Psychiatry, Medical University of Warsaw, Warsaw, Poland

[4] Department of Psychiatry, University of Michigan, Ann Arbor, MI 48109

[5] Department of Psychology, University of New Mexico, Albuquerque NM 87131

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***Corresponding Author:**
Scott Edwards, PhD
Department of Physiology
LSU Health Sciences Center
1901 Perdido Street, MEB 7205
New Orleans, LA 70112

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Abstract

Alcohol use disorder (AUD) and chronic pain are enduring and devastating conditions that share an intersecting epidemiology and neurobiology. Chronic alcohol use itself can produce a characteristic painful neuropathy, while the regular analgesic use of alcohol in the context of nociceptive sensitization and heightened affective pain sensitivity may promote negative reinforcement mechanisms that underlie AUD maintenance and progression. The goal of this

review is to provide a broad translational framework that communicates research findings spanning preclinical and clinical studies, including a review of genetic, molecular, behavioral, and social mechanisms that facilitate interactions between persistent pain and alcohol use. We also consider recent evidence that will shape future investigations into novel treatment mechanisms for pain in individuals suffering from AUD.

Introduction

Alcohol use disorder (AUD) and chronic pain are frequent, debilitating, and persistent conditions associated with significant individual and social costs (Zale et al., 2015). AUD and chronic pain also commonly co-occur, share many of the same neural substrates, and may also exacerbate neural dysfunction associated with pain transmission, alcohol intoxication, and alcohol withdrawal (Apkarian et al., 2013, Egli et al., 2012, Robins et al., 2019). The goal of this critical review is to extend recent reviews on the topic of alcohol and pain (Egli et al., 2012, Zale et al., 2015). Here, our aim is to establish a broader translational focus that provides an update on recent models and findings from preclinical and clinical studies, including a review of molecular, genetic, behavioral, and social mechanisms that may underlie pain and alcohol use and dependence across species. We also consider the evidence for informing treatment recommendations and future research at the intersection of alcohol and pain.

Chronic Pain Prevalence and Costs

Chronic pain, defined as pain that lasts longer than three months, is estimated to impact at least 20% of all individuals in the United States (U.S.; (Dahlhamer et al., 2018), Europe (Breivik et al., 2006), and in other countries worldwide (Goldberg and McGee, 2011). As implied by the name, chronic pain tends to be persistent and debilitating, and few people report "recovery," as defined by a complete absence of pain, even after several years of seeking treatment (Elliott et al., 2002). The impact of pain on health, functioning, and quality of life is profound with devastating effects on social, physical, psychological, and occupational functioning (Goldberg and McGee, 2011). Growing worldwide acknowledgement of disability associated with chronic pain will be recognized in the newest version of the International Classification of Diseases, 11th edition (ICD-11), which will include the diagnosis of chronic pain for the first time (Nugraha et al., 2019), including chronic primary pain (e.g., chronic headache pain) and chronic secondary pain (e.g., musculoskeletal pain due to inflammation). The price of chronic pain is staggering, with direct healthcare costs in the U.S. estimated to range from $300 billion up to at least $600 billion per year when including costs associated with workplace productivity loss (Gaskin and Richard, 2012).

Alcohol Use Disorder Prevalence and Costs

Excessive alcohol consumption and AUD are leading causes of morbidity and mortality with enormous societal costs (Bouchery et al., 2011). Well over 3 million deaths worldwide each year are attributable to alcohol, and alcohol contributes to over 5% of the global burden of disease (World Health Organization, 2018). In the U.S., it has been estimated that approximately 10-13% of individuals meet criteria for a current (past 12 months) AUD (Grant et al., 2017, Substance Abuse and Mental Health Services Administration, 2018) and up to one-third of all adults in the U.S. will meet criteria for a lifetime AUD (Grant et al., 2017). Over 88,000 people die each year in the U.S. due to alcohol-related causes, making alcohol the fourth leading cause of preventable death in the U.S. (Stahre et al., 2014). Given the widespread prevalence, it is not surprising that excessive alcohol use and AUD are also costly. Estimates in the U.S. and Europe are staggering, with approximately $249 billion U.S. dollars (Sacks et al., 2015) and $125 billion Euros spent annually (Anderson and Baumberg, 2006). Most of the costs associated with alcohol use and AUD are due to workplace productivity loss, although health care expenses, law

enforcement and criminal justice system costs, and costs due to accidents and motor vehicle crashes also contribute (Sacks et al., 2015).

Comorbidity of Problematic Alcohol Use and Pain

Epidemiological data indicates a strong association between chronic pain and AUD (Beasley et al., 2016), although directionality is difficult to assess (Macfarlane and Beasley, 2015). Prospective examinations of wave one and wave two data from the National Epidemiological Survey on Alcohol and Related Conditions (NESARC) found that pain interference prospectively predicted the development of AUD (McDermott et al., 2018), and decreases in alcohol consumption were associated with reductions in ratings of acute pain severity three years later (Imtiaz et al., 2018). Acute pain frequency (i.e., days with pain) is also associated with diagnosis of AUD (Edlund et al., 2013). Individuals with chronic pain tend to report higher levels of alcohol use and AUD than the general population (Hoffmann et al., 1995, Vowles et al., 2018) and also report using alcohol to medicate acute pain symptoms (Alford et al., 2016, Brennan et al., 2011, Riley and King, 2009). Likewise, at least one-third to more than one-half of individuals seeking treatment for AUD report chronic, recurrent pain (Boissoneault et al., 2019, Caldeiro et al., 2008, Jakubczyk et al., 2015).

Genetic Mechanisms in the Association between Pain and Alcohol Use

Twin studies indicate that up to half of the variability in both AUD and chronic pain may be explained by genetic factors, indicating a large genetic component for both conditions. A comprehensive review of genome-wide association studies (GWAS) and candidate gene association studies (CGAS) that may explain the comorbidity between AUD and chronic pain was recently published (Yeung et al., 2017). The review specifically highlighted genes related to dysregulation of reward and stress systems (e.g., *TBX19*), genes involved in modulating reward and stress systems (e.g., *ADRA1A, HTR7*), and those genes that have involvement in the CNS, more broadly (e.g., *CDH13*). The review also noted the limitation of many prior studies being underpowered to reach the threshold of genome-wide significance. More recent studies that have included much larger sample sizes to detect genome-wide effects include a recent analysis of problem drinking and AUD (Kranzler et al., 2019), chronic back pain (Suri et al., 2018), and headache (Meng et al., 2018), yet polymorphisms that reached genome-wide significance in these larger studies were not overlapping across studies.

To our knowledge, no studies have examined genetic variants associated with the comorbidity of AUD and chronic pain in human samples. Yet, a few recent studies have expanded on the prior review by Yeung and colleagues (2017). An examination of genetic contributions to postoperative pain control across 42 studies concluded AUD was associated with genetic polymorphisms involved with pain sensitivity (Elmallah et al., 2018). Using a case-control design, Lee and colleagues (2018) found phosphatidylinositol 4-phosphate 5 kinase type 1C (*PIP5K1C*) gene, which regulates pain signaling and sensitization (Wright et al., 2014), to be associated with AUD among African Americans in a discovery sample. Thus, genetic variants in PIP5K1C may be one potential mechanism for the comorbidity of AUD and chronic pain.

Sex Differences in the Association between Pain and Alcohol Use

Sex differences in chronic pain are profound, albeit not well understood (Mogil, 2012). Women are more likely to develop chronic pain, are more sensitive to pain in controlled laboratory studies, and may be at higher risk of developing persistent pain after injury (Linnstaedt et al., 2015, Rosen et al., 2017, Sorge and Totsch, 2017). Sex differences in alcohol use are also notable and complex. Women tend to drink less alcohol than men, although the differences in rate of drinking and heavy drinking by sex is narrowing in recent years (Grant et al., 2017, Khan et al., 2013). Yet, women with AUD tend to have more severe consequences, particularly medical and psychiatric comorbidities as compared to men (Agabio et al., 2017). There are also racial and ethnic differences in pain perception, assessment, and treatment (Campbell and Edwards, 2012), and racial and ethnic differences in alcohol use, AUD, and treatment (Vaeth et al., 2017, Williams et al., 2016). Intersectionality of sex and racial/ethnic differences have also been examined in chronic pain (Forsythe et al., 2011, Meints et al., 2018) and AUD (Glass et al., 2017, Witbrodt et al., 2014). Yet, to our knowledge, only a few studies have explored sex, race, or the intersection of sex and race in the association between pain and AUD.

In samples of older adults, Brennan and colleagues found pain to be associated with lower rates of alcohol use and less drinking over time, but more alcohol-related problems, particularly among African Americans (Brennan and Soohoo, 2013) and males (Brennan et al., 2011). Among both men and women, problem drinking in older adulthood was associated with greater pain and greater use of alcohol to manage pain symptoms, which was further associated with worse health outcomes among men and more drinking problems among women (Brennan et

al., 2005). Among younger adults, ages 25 to 45, there is experimental evidence that acute alcohol (approximate BAC = 0.065) may be associated with increased pain threshold among women, and that subjective response to alcohol may be more strongly associated with ratings of pain relief following alcohol administration among women (Hill et al., 2018). Yet, there is also evidence that men with chronic pain may be more at risk of AUD and depression, as well as report a stronger association between pain, depression, and alcohol use, as compared to women (Barry et al., 2013, Brown, 2015, Manubay et al., 2015). Also, in a sample of adults with chronic pain, pain-related anxiety was positively associated with alcohol-related consequences and symptoms of alcohol dependence among males, but not females (Zale et al., 2019).

More Questions than Answers Regarding the Associations between Pain and AUD in Humans

The association between pain and alcohol use is clearly complex, and the mechanisms of comorbidity of chronic pain and AUD are not well understood in humans. There is a literature examining analgesic effects of alcohol (Chung and Wang, 2013, Hill et al., 2018, Patberg et al., 1999, Woodrow and Eltherington, 1988, Thompson et al., 2017) and recent empirical work has found acute pain increases the urge to drink (Moskal et al., 2018). Further, preliminary work indicates greater alcohol consumption is associated with momentary reductions in pain (Carpenter et al., 2018). It is also the case that alcohol may exacerbate painful conditions. For example, alcohol is a leading cause of chronic pancreatitis, which is associated with severe abdominal pain (Conwell et al., 2014). Alcohol also increases risk of accidental injuries, including a greater likelihood of bone fractures, while alcohol may also inhibit proper recovery of fractures (Richards et al., 2017). Heavier alcohol use at the time of injury may also increase the risk of developing chronic pain (Castillo et al., 2006).

Yet, to our knowledge, it is unclear if alcohol continues to provide analgesic effects among those with chronic pain and AUD, or whether alcohol could increase pain hypersensitivity among those with more severe AUD, as seen in the preclinical models, discussed in the next section. Importantly, few studies in humans have directly studied patients with chronic pain and AUD who did not have other comorbidities (e.g., depression, opioid use disorder). Thus, looking to the refinement and utilization of preclinical models is important for gaining a better understanding of the mechanisms that may underlie the interaction of pain and AUD.

Preclinical Models to Investigate the Intersection of AUD and Pain Mechanisms

Preclinical models provide a valuable tool for studying certain key aspects of AUD-related symptoms, including pain-like behaviors. Rodent models in particular have been critical to our understanding of the neurobiology of pain and AUD and have directly impacted the availability of treatments for these conditions. In this section, we describe rodent models that are the most frequently used to study pain. We then describe the most commonly used rodent models for studying AUD. Finally, we discuss recently discovered interactions between pain and AUD from the utilization of these models. Only the most commonly used pain and AUD models are described. The general discussion of these models is not intended to be exhaustive. For comprehensive reviews on rodent models of pain (Deuis et al., 2017; Le Bars et al., 2001; Mogil et al., 2010), AUD (Tunstall et al., 2019), and the interaction between pain and AUD (Egli et al., 2012; Apkarian et al., 2013), please refer to the suggested literature.

Rodent Models of Pain

Pain is defined as an unpleasant sensory and emotional experience that is associated with actual or potential tissue damage or described in terms of such damage (International Association for the Study of Pain). This classification implies that pain is a subjective, emotional experience and thus cannot be directly measured in rodents. A term that is commonly used in rodent models is "nociception," which is not synonymous with pain. Nociception (from the Latin *nocere*, "to harm or hurt") refers to the process of the transmission of noxious signals (e.g., potentially damaging levels of heat, cold, pressure, or chemicals) by nociceptors ("noci"=noxious; "ceptor"=receptor) to the brain. For simplicity, we use the terms "pain-like" and "nociception" interchangeably herein when referring to rodent models. Allodynia (i.e., a pain response to normally non-noxious stimuli) and hyperalgesia (i.e., an exacerbated pain response to normally noxious stimuli) are also discussed, particularly in the context of alcohol withdrawal-induced allodynia/hyperalgesia. Several rodent models have been developed to mimic acute and chronic pain conditions in humans and study pain's underlying neurobiological mechanisms. Quantitative and qualitative aspects of nociception and alterations of physiology during acute and chronic pain-like states can be measured. Different forms of nociception (e.g., mechanical, thermal, and chemical) can be induced in rodents, the intensity of which can be systematically

measured (Deuis et al., 2017). These tests of pain-like states allow researchers to study the mechanisms that are responsible for nociception and test the analgesic efficacy of various approaches (e.g., a drug/medication) to alleviate pain. We briefly describe tests of thermal and mechanical sensitivity that are the more commonly used models of nociception.

Rodent Models of Thermal and Mechanical Sensitivity

An important aspect of alcohol dependence, alcohol withdrawal, and chronic pain in humans are changes in thermal and/or mechanical sensitivity, both of which can be evaluated in rodent models using the well-established tail-flick test (D'Amour and Smith, 1941), hot-plate test (Woolfe and Macdonald, 1944), Hargreaves test (Hargreaves et al., 1988), von Frey test (Chaplan et al., 1994), and Randall-Sellito test (Randall and Sellito, 1957).

Models of thermal hyperalgesia are mostly utilized to evaluate inflammatory pain, but animals with neuropathic pain have been shown to exhibit greater sensitivity to thermal stimuli. In the tail-flick model, the rodent's tail is dipped in hot water (50-56°C) until it retracts its tail. Alternatively, radiant heat (i.e., from a light source) is applied until the tail is retracted. The latency to tail retraction is recorded as a measure of nociception. The maximum duration of exposure to the heat stimulus depends on the temperature (e.g., 20 s for 54°C) to prevent the risk of tissue damage. The tail withdrawal response is generally considered a spinal reflex (Gregory et al., 2013). In the hot-plate test (50-56°C), the animal is placed on a hot plate that has an acrylic cylindrical "enclosure" that minimizes the animal's movement. Behavioral responses, such as licking the hind paws and jumping, are commonly used indices of nociception (Vendruscolo et al., 2004). A cutoff (e.g., 20 s for 54°C) is set to ensure that no tissue damage occurs. A nociceptive response in the hot-plate test is considered to be supraspinally mediated (Gregory et al., 2013). A caveat is that repeated testing in the hot-plate changes the rats nociceptive responses due to habituation and learning (Vendruscolo et al., 2004). The Hargreaves test is also commonly used in rodents. Rodents are habituated (e.g., for 15 min) to an apparatus that consists of a glass pane upon which the rodent is placed. The rodent is unrestrained, but a transparent acrylic enclosure limits its movements. A moveable infrared generator is placed below the glass pane, and heat is directed toward the hind paw until the animal retracts the paw.

Another common mode of sensitivity investigated is mechanical. In the von Frey model, animals are placed in cages with grid floors that allow access to the paws. After a habituation period, calibrated filaments are applied perpendicularly to the plantar surface of the rodent's paw (most commonly the hind paw), starting from a lower force to a higher force until the animal withdraws its paw. An up-down schedule of forces can be used to determine the paw withdrawal threshold, which is used as an index of mechanical sensitivity (Edwards et al., 2012). Electronic von Frey equipment is also available. In this case, a single testing probe is used, and an electronic device detects the amount of force that is necessary for paw withdrawal. Neither the manual nor electronic probes damage the skin or cause lasting pain. Similarly, the Randall-Selitto test applies an increasing amount of mechanical force to either the fore or hind paws and the withdrawal response is measured (Randall and Sellito, 1957). For all of the tests described above, painful conditions often lead to lower thresholds, whereas analgesia (antinociception) leads to higher thresholds. Hyperalgesia and allodynia are associated with lower response thresholds. The tail-flick and hot-plate tests are most commonly used to evaluate the analgesic efficacy of drugs, whereas the Hargreaves and von Frey tests are used to evaluate both analgesia and pain-like states (hyperalgesia/allodynia). However, based on the considerable lack of translational efficacy of putative analgesics as examined via these preclinical methods, many researchers are now transitioning away from reflex-based assays toward more cognitive and motivational tasks that are thought to be more related to the negative affective components of pain (e.g., Pahng and Edwards, 2018; Tappe-Theodor et al., 2019).

Rodent Models of Alcohol Use Disorder

As for any complex disorder, rodent models do not recapitulate all aspects of AUD or chronic pain. However, important features of AUD can be modeled in rodents (Vendruscolo and Roberts, 2014; Tunstall et al., *in press*). Different levels of alcohol intoxication produce physiological and behavioral alterations, such as hypothermia, motor incoordination, anxiolysis, tolerance, and sedation. During withdrawal, such somatic symptoms as hyperthermia, anxiogenesis, tremor, and seizures may be observed. For a comprehensive review of rodent models of AUD, see Tunstall et al. (*in press*). Important for the present review, alcohol intoxication and withdrawal typically produce analgesia and hyperalgesia, respectively; these aspects of AUD are discussed in the next section.

Perhaps the most important aspect of models of AUD is voluntary alcohol self-administration to the point of achieving a relevant pharmacological effect. Richter and Campbell (1940) reported that laboratory rats voluntarily consume alcohol when given access to a bottle of water and a bottle of alcohol, a model that is popularly known as the two-bottle choice test. In this model, continuous access to *ad libitum* alcohol (e.g., 24 hours/day) and water typically yields highly fluctuating levels of alcohol consumption. Adaptation of this model has been used to model binge drinking, which is defined by the National Institute on Alcohol Abuse and Alcoholism as an excessive pattern of drinking that leads to blood alcohol levels (BALs) above 80 mg/dl. The use of sweeteners in combination with alcohol to make the solution more palatable to rodents (Ji et al., 2008) has been found to produce such BALs. Other variants of the two-bottle choice model use intermittent 24-hour access to alcohol (e.g., on Mondays, Wednesdays, and Fridays; Fredriksson et al., 2017; Wise, 1973; Simms et al., 2008) or access to alcohol during the animal's dark (active) cycle (i.e., the drinking-in-the-dark model; Holgate et al., 2017; Thiele and Navarro, 2014), which lead to higher BALs than continuous access to alcohol, in most cases generating peak BALs above 80 mg/dl. However, a major drawback of two-bottle choice procedures is the difficulty in determining when and for how long animals reach relevant BALs. Also, while these models are useful because binge drinking is a common and harmful pattern of alcohol use, they have limited utility in the study of alcohol consumption during alcohol dependence.

To study alcohol dependence, a liquid diet protocol was proposed (Lieber and DeCarli, 1982) where animals are given access to a nutritionally balanced diet that contains alcohol as their sole source of calories. The control group is given a calorically matched diet without alcohol. Both groups are given *ad libitum* access to water. There are no standardized procedures for the alcohol liquid diet across laboratories, and the concentration of alcohol in the diet varies considerably (e.g., 5-35%). However, this unique approach results in BALs that are sufficient to induce liver damage, intoxication, tolerance, dependence, and withdrawal (Lee et al., *in press*; Gilpin et al., 2009). Equally effective in producing alcohol dependence is the chronic, intermittent alcohol vapor exposure model, where animals are typically exposed to alcohol vapor for 14 hours/day (intoxication), followed by 10 hour with vapor off (withdrawal). Control rats are exposed to air. Food and water are freely available during alcohol vapor exposure. In both the liquid diet and vapor models, the animals in the alcohol group can reach BALs above 200 mg/dl

(i.e., ~2.5-times binge drinking levels) and exhibit motivational signs of withdrawal (e.g., anxiety-like behavior and increase in alcohol drinking during withdrawal) as well as somatic signs of withdrawal (e.g., ruffled fur, porphyrin staining around the eyes, tremor, and abnormal posture; Vendruscolo and Roberts, 2014; Gilpin et al., 2008). A considerable drawback of the liquid diet and vapor models is their forced (i.e., non-contingent) method of alcohol administration, although both models can be combined with operant self-administration to measure volitional alcohol intake, the motivation for alcohol, and compulsive-like alcohol consumption despite punishment. Both models also allow for the maintenance of high BALs over extended periods of time to reliably model dependence symptoms.

Interaction between Alcohol Dependence and Pain-Like Behavior

Gatch and Lal (1999) performed a seminal set of studies describing the anti-hyperalgesic effects of alcohol in the context of alcohol withdrawal-induced hyperalgesia. Levine and colleagues exended these original investigations to investigate mechanism, using male Sprague-Dawley rats given a Lieber-DeCarli alcohol (6.5%) liquid diet for 12 weeks (Dina et al., 2000, 2006, 2008). Alcohol-exposed rats exhibited hyperalgesia for 4-12 weeks in the Randall-Sellito test compared with controls. Alcohol-exposed rats also exhibited mechanical hypersensitivity in the von Frey test and thermal hyperalgesia in the Hargreaves test after 8 weeks of alcohol exposure compared with control rats. Mechanical hypersensitivity in alcohol-exposed rats increased at 5 weeks after the cessation of alcohol, indicating the long-lasting allodynic effects of alcohol withdrawal. Pain-like hypersensitivity was found to be mediated by protein kinase Cε (Dina et al., 2000, 2006). In another study, Dina et al. (2008) reported that adrenal medullectomy or the blockade of β_2-adrenergic receptors on nociceptors in male Sprague-Dawley rats that were subjected to an intermittent alcohol liquid diet procedure (4 days on the diet and 3 days off the diet) prevented/reversed alcohol withdrawal-induced hyperalgesia. β-adrenergic receptor antagonism was shown to decrease alcohol self-administration in alcohol vapor-exposed dependent rats (Gilpin et al., 2010). In addition to participation of the sympatho-adrenal axis, daily systemic administration of the glucocorticoid receptor antagonist mifepristone (30 mg/kg) blocked the development of alcohol withdrawal-induced mechanical hyperalgesia. Once hyperalgesia had already been established, repeated, systemic injections of mifepristone and an

acute intradermal injection of mifepristone reversed alcohol withdrawal-induced hyperalgesia (Dina et al., 2008). Chronic mifepristone administration was also shown to block the escalation of alcohol drinking in rats that were exposed to alcohol vapor (Vendruscolo et al., 2012). Moreover, acute mifepristone administration reversed the escalation of alcohol drinking in dependent rats (alcohol vapor), without affecting alcohol drinking in nondependent rats (Vendruscolo et al., 2015). Furthermore, chronic mifepristone treatment decreased alcohol drinking in humans with alcohol use disorder (Vendruscolo et al., 2015). These findings suggest that glucocorticoid receptors play a functional role in dependence-induced pain-like behavior and alcohol drinking.

Using the alcohol vapor model of dependence, Edwards et al. (2012) reported that dependent male Wistar rats exhibited mechanical hypersensitivity, indexed as lower paw withdrawal thresholds in the von Frey test, compared with nondependent rats. Notably, rats that were exposed to alcohol vapor for 4 weeks did not exhibit mechanical hypersensitivity. Only after 8 weeks of alcohol vapor exposure, when BALs were ~200 mg/dl, was mechanical hypersensitivity detected. These findings suggest that alcohol withdrawal-induced allodynia depends on the amount of alcohol exposure. The treatment of rats with a corticotropin-releasing factor-1 (CRF_1) receptor antagonist reversed alcohol withdrawal-induced mechanical hypersensitivity. A CRF_1 receptor antagonist also decreased alcohol drinking in dependent but not nondependent rats in the alcohol vapor model (Funk et al., 2007), suggesting common dysregulation of the CRF system that contributes to allodynia and the escalation of drinking. Chronic intermittent alcohol vapor exposure is typically experimenter-controlled, and alcohol consumption can be assessed under operant self-administration conditions during withdrawal. However, de Guglielmo et al. (2017) recently developed a model in which male Wistar rats voluntarily self-administer alcohol vapor. The rats were allowed to nosepoke for access to alcohol vapor in 8 hours sessions that were conducted every other day. Rats escalated their alcohol vapor self-administration and reached BALs > 200 mg/dl. Similar to passive alcohol vapor exposure, the rats exhibited increase in alcohol intake and the motivation for alcohol compared with rats that did not escalate alcohol self-administration. Additionally, escalated rats exhibited mechanical hypersensitivity in the von Frey test. Again, relatively high BALs (i.e., ~200 mg/dl) were necessary to produce allodynia, a result that was consistent with the passive alcohol vapor model.

Alcohol-induced hyperalgesia can also be observed in mouse models (Alongkronrusmee et al 2016; Bergeson et al 2016; Smith et al 2016), which allows for powerful genetic manipulations. For example, Alongkronrusmee and colleagues (2016) recently reported that male wildtype (WT) and δ-opioid receptor (DOR) knockout C57BL/6 mice that were allowed to self-administer alcohol (10%) versus water for 3 weeks in a two-bottle choice drinking-in-the-dark (4 hours/day) procedure exhibited escalation of alcohol intake to ~4 g/kg in 4 hours. A few days into alcohol abstinence, both groups exhibited mechanical hypersensitivity in the von Frey test, but this effect was exacerbated in DOR knockout mice. Using a method of passive alcohol delivery, in which mice received 2 or 3 g/kg (20%) alcohol via oral gavage (i.e., feeding tube) for 15 sessions, mice that received 3 g/kg alcohol exhibited significant allodynia compared with the mice that received 2 g/kg alcohol when tested during alcohol withdrawal (24 hours). The intrathecal administration of clonidine, an α_2-adrenergic receptor agonist that is used to treat alcohol withdrawal in humans, reversed alcohol withdrawal-induced allodynia. Notably, allodynia persisted for 4-7 days in mice that voluntarily drank alcohol, whereas it persisted for 4 weeks in mice that received higher doses of alcohol via gavage. Again, DOR knockout mice exhibited exacerbated allodynia compared with WT mice. The pharmacological blockade of DORs with naltrindole in alcohol-naïve mice produced an allodynic effect, and a low dose of naltrindole that did not produce allodynia *per se* prolonged the duration of alcohol withdrawal-induced allodynia. These findings provide evidence of the participation of DORs (and α_2-adrenergic receptors in the spinal cord) in mediating alcohol withdrawal-induced allodynia.

We discussed above the effects of chronic alcohol exposure on pain-like behavior. Another intriguing research question is the effects of pain-like conditions on alcohol drinking, and a few recent studies have begun to address this relationship. González-Sepúlveda et al. (2016) induced a chronic neuropathic pain-like state via partial sciatic nerve ligation in male CD1 mice. Cold and mechanical allodynia confirmed a pain-like state in mice with partial sciatic nerve ligation (compared with sham-operated, control mice). Sciatic nerve-ligated mice also exhibited increases in anxiety- and depression-like behavior compared with control mice. Using the two-bottle choice drinking-in-the-dark paradigm, mice in a pain-like state consumed significantly greater, albeit transitory, amounts of alcohol compared with control (non-pain) mice. These animals had not been exposed to alcohol before surgery. However, alcohol drinking did not alleviate thermal allodynia that was associated with the neuropathic pain-like state. Butler

and colleagues (2017) also found increased levels of drinking in male C57BL/6J mice following surgical destabilization of the medial meniscus, a model of osteoarthritis. The findings that are discussed above clearly indicate that rodents exhibit many aspects of pain and AUD that are also observed in the human condition. Exposure to alcohol, either voluntarily or passively, may lead to the escalation of alcohol drinking and promote pain-like behaviors. Pain-like conditions may in turn also lead to an increase in alcohol drinking. However, exposure to high amounts of alcohol, which may be challenging in models of voluntary drinking, appears to be critical for the reliable detection of hyperalgesia-like behaviors.

Finally, as mentioned above the motivational and affective components of pain have started to be more thoroughly investigated in rodent models. A potential model for this purpose was recently described by Pahng and Edwards (2018). This model incorporates a non-reflex-based method to measure pain avoidance-like behavior in rats. The model consists of exposing animals to a bright compartment that is naturally aversive to rodents. To escape from this environment, the rodent needs to run across probes of varying heights to reach a dark, less aversive compartment. The latency to exit onto the nociceptive probes is used as index of pain avoidance-like behavior, which is expected to be longer in animals in a pain-like state. Use of this test in animals experiencing drug and alcohol withdrawal might be challenging because withdrawal produces both anxiety- and pain-like behaviors, which are opposite motivational components of this model. However, Pahng and colleagues (2017) revealed increases in pain avoidance-like behavior in opioid-dependent animals under conditions that did not produce differences in anxiety-like behavior in this test. This study also revealed significant, yet modest, correlations in hyperalgesia-like behaviors measured via von Frey versus pain avoidance tests, suggesting that these two measures detect overlapping yet potentially distinct aspects of pain-related behaviors in animals. Behavioral measurement of the differential contributions of somatic versus motivational/affective components of pain may also correspond to distinct neurobiological substrates, and these relationships likely have important ramifications for future therapeutic strategies.

Preclinical Findings in Rodent models of Alcohol Dependence and Hyperalgesia

Ascending and descending nociceptive circuitry intimately interacts with the neural substrates of alcohol reinforcement (Egli et al., 2012). The search for neurobiological correlates of hyperalgesia in the context of alcohol dependence has recently discovered several new mechanisms and promising targets for medications development for both pain and AUD. As one example, Ye and colleagues have performed an extensive set of studies focused on the lateral habenula (LHb) using a chronic, intermittent alcohol-drinking paradigm (Fu et al., 2015). The LHb is implicated in the regulation of aversive behaviors, and is therefore well positioned to mediate important aspects of negative affect associated with alcohol withdrawal and drinking to relieve negative affect states. Glutamatergic neurotransmission and hyperexcitability of the LHb is manifest during withdrawal, and this process appears to be driven by enhanced functions of TRPV1 vanilloid receptors (Gregor et al., 2019) and suppression of M-type potassium channels (Kang et al., 2019). One viable therapeutic target in the LHb mediating AUD symptoms is the orphan G protein-coupled receptor GPR139 (Kononoff et al., 2018). Antagonism of GPR139 with JNJ-63533054 reduced both escalated drinking and hyperalgesia symptoms in alcohol-dependent rats. The endogenous ligand for GPR139 is unclear at the present time, but may relate to either tryptophan/serotonin signaling (Liu et al., 2015), adrenocorticotropic hormone (ACTH), and/or melanocyte-stimulating hormone (Nohr et al., 2017).

Stimulation of endogenous cannabinoid systems represents another emerging area of analgesic development, along with some very promising preliminary studies. As one example, systemic CB2 receptor stimulation alleviates hyperalgesia symptoms in an animal model of chronic pancreatitis pain induced by an alcohol/high fat diet (Zhang et al., 2014). Because CB2 receptors are predominantly distributed outside of the central nervous system, targeting these receptors may produce fewer undesireable psychotropic side effects. Endocannabinoid signaling might reduce pain-like symptoms due to their stress-buffering capacities (Morena et al., 2016) or via anti-inflammatory actions (Katz et al., 2015). Targeting systemic inflammatory processes via endocannabinoid signaling or other processes would appear to be a highly valuable strategy, although sex differences may need to be more closely investigated. For example, the tetracycline derivative tigecycline was found efficacious in reducing mechanical and thermal hyperalgesia in binge-drinking male mice, although this treatment actually increased pain-like sensitivity in females (Bergeson et al., 2016). Although the precise mechanism of tigecycline is still debatable (Oliveros and Choi, 2017), these findings highlight vital importance of investigating sex as a

factor in all pain studies, especially given the fact that females are disproportionately affected across most pain syndromes. Bergeson and colleagues recommended additional studies to clarify inflammatory or other mechanisms that may drive the sex-disparate effects of tigecycline. In a similar vein, Kash and colleagues recently discovered that CFA inflammation increased hyperalgesia in both male and female mice, but increased alcohol drinking only in males (Yu et al., 2019). Thus, a better understanding of basic pain-alcohol interactive mechanisms driving sex differences in females versus males is warranted and will likely produce more breakthroughs for the benefit of both sexes.

Emerging Circuitry & Molecular Signatures of Alcohol Withdrawal Hyperalgesia

A majority of the previous work examining the neurobiology of alcohol has focused on the investigation of individual brain regions, although how central stress and nociceptive circuits are engaged and potentiated in the state of alcohol dependence is a rapidly developing area of preclinical research. Recent work from our group showed that alcohol dependent rats exhibit weaker connectivity between the central amygdala (CeA) and ventrolateral periaqueductal gray during withdrawal. Furthermore, optogenetic activation of vlPAG-projecting CeA neurons attenuates alcohol withdrawal hyperalgesia whereas inhibition of vlPAG-projecting CeA neurons produces thermal hyperalgesia in otherwise experimentally naïve animals (Avegno et al., 2018). The goal of circuit level analysis of alcohol-related hyperalgesia should be to facilitate the identification of potential treatment targets in humans with AUD living with pain. This can be achieved by establishing the molecular signature of cells that modulate pain and nociception via projections to specific downstream brain regions. If specific receptor subtypes are preferentially enriched on specific sets of projection neurons, then pharmacological modulation of those receptors may present a unique opportunity to modulate that circuit for reducing pain-like outcomes with minimal off-target effects. Focusing on the CeA as one potential example, chronic alcohol exposure and withdrawal alters MC4R expression in CeA, and site-specific antagonism of MC4Rs in CeA reverses alcohol withdrawal hyperalgesia (Avegno et al., 2018). MC4Rs are expressed at most levels of the ascending and descending pain circuitry and may induce plasticity via effects on AMPA receptor trafficking to the membrane (Caruso et al., 2014); therefore, it would be of interest to know whether MC4R expression is enriched

specifically in cells linking these pain modulation regions (e.g., on the post-synaptic membranes of vlPAG-projecting cells in the CeA). This information may be especially impactful because prior work showed that intra-nasal delivery of an MC4R antagonist blocks alcohol withdrawal hyperalgesia (Roltsch-Hellard et al., 2017). The corticotropin-releasing factor type-1 receptor (CRFR1) may be similarly leveraged to modulate specific circuits for reducing pain in individuals with AUD. For example, CRF and CRFR1 mRNA and protein levels are highly expressed in the CeA (e.g., Funk et al., 2006), CRFR1 modulation of CeA synaptic transmission is altered by alcohol dependence (Roberto et al., 2010), and CRFR1 antagonism in CeA reverses hyperalgesia induced by nicotine dependence and predator odor stress (Baiamonte et al., 2014; Itoga et al., 2016). It remains to be determined whether CRFR1 effects in CeA on hyperalgesia can be attributed to their expression on specific subsets of CeA projection cells. Future work will undoubtedly build on these initial circuit-level findings and also identify roles for new as yet unidentified circuits in alcohol withdrawal hyperalgesia.

Social Aspects of Pain in the Context of Alcohol

In addition to pain relief, the facilitation of social interaction is another important reinforcing property of alcohol, including the emotional construct of empathy in the context of pain. In a recent study, the neural substrates mediating the enhancement of empathetic-like behavior by alcohol were investigated (Sakaguchi et al., 2018). This study found that observation of mice receiving foot shocks recruited subsets of neurons in the anterior cingulate cortex (ACC) that also corresponded to experiences of pain in the observer mouse. This phenomenon was further strengthened by alcohol (1.5 g/kg), although the non-contingent nature of alcohol administration may limit the applicability of findings. These data complement a series of investigations in drinking animals suggesting that alcohol withdrawal-induced hyperalgesia may also be transmitted to conspecifics (Smith et al., 2016; Walcott et al., 2018). Indeed, the social transfer of hyperalgesia may represent an adaptive biobehavioral process to facilitate the communication of dangers within a group of animals. Interestingly, chemogenetic inactivation of the ACC reduced hyperalgesia symptoms in both alcohol-exposed mice and their bystander partners (Smith et al., 2017). These recent insights demonstrate the preclinical potential to

536 investigate important social components of affective pain that may directly relate to the
537 fundamental reinforcing properties of alcohol in human populations.

538

539 **Clinical Models to Investigate the Intersection of AUD and Pain Mechanisms**

540 As noted above, there have been few clinical studies examining chronic pain and AUD
541 populations, and more work is needed to explore this comorbidity in human samples. Given the
542 available preclinical and clinical models of pain and alcohol use, there is great potential to bridge
543 bench to bedside in informing future treatment strategies and new research directions for
544 understanding the comorbidity of chronic pain and AUD. In this section we review approaches
545 to studying pain and alcohol use in humans and have attempted to align, when possible, with the
546 preclinical approaches, described above.

547 *Clinical Models of Pain*

548 Unlike preclinical models of pain, it is not ethical to randomly assign individuals to have
549 a chronic pain condition, thus most studies of pain induction in humans are based on acute pain
550 manipulations or provoked sensitization models that are designed to mimic aspects of
551 neuropathic pain. Importantly, human experimental pain models provide a bridge to preclinical
552 pain models and provide the opportunity to evaluate mechanisms of pain severity, pain
553 sensitization, and analgesia. Similar to the preclinical models, human experimental pain models
554 can also be characterized by targeting mechanical stimulation (e.g., von Frey filaments use to pin
555 prick, pressure applied via pinching or algometry of the muscles), thermal stimulation (e.g., cold
556 pressor, radiant heat and burn injury), and chemical stimulation (e.g., capsaicin injection or
557 topical application, mustard oil, hypertonic saline injections), yet each model of experimental
558 pain has shortcomings (Reddy et al., 2012). Further, the lack of a chronic pain experimental
559 model is a limitation of clinical research and necessitates that associational studies conducted
560 with chronic pain patients are still critical for gaining insights into chronic pain and comorbid
561 conditions.

562 *Clinical Models of Alcohol Use Disorder*

563 Similarly, it is not ethical to randomly assign individuals to have an AUD, thus most
564 experimental studies of alcohol use in humans are based on human laboratory studies of alcohol
565 self-administration, alcohol challenge studies, and studies of alcohol cue- and stress-reactivity

(Ray et al., 2018, Yardley and Ray, 2017). Experimental studies involving alcohol administration are typically conducted with non-treatment seeking individuals or drinkers without AUD (Enoch et al., 2009), however, there are several measures that can be informative for research into the clinical characteristics of AUD, including subjective response to alcohol, self-reported craving for alcohol, amount of alcohol consumed or self-administered versus placebo controls, and cue-induced or stress-induced drinking behavior (Litten et al., 2012). Double-blind placebo-controlled alcohol administration studies (either self administered or experimenter administered) are the gold standard for assessing alcohol's pharmacological effects and craving or subjective response to alcohol, given known alcohol expectancy effects that could be present in unblinded or uncontrolled studies (Stacy et al., 1990). Similar to the case of chronic pain, ethical concerns about alcohol administration among patients with AUD means it is critical that associational studies are conducted among patients with AUD when asking questions about the intersection of pain and alcohol use among individuals with AUD.

Interaction between Alcohol Use and Pain in Humans

Older laboratory-based studies have examined analgesic effects of alcohol in humans (Stewart et al., 1995, Brown and Cutter, 1977, Cutter et al., 1979, Cutter et al., 1986) and have generally found that alcohol reduces acute pain (Thompson et al., 2017). Expectancies for pain reduction partially explained the effects in these prior studies (Egli et al., 2012). More recent studies, using placebo-controlled designs have found additional evidence that alcohol produces analgesic effects, which may be moderated by family history of AUD and neuroticism (Ralevski et al., 2010). Yet, these prior studies have focused on acute pain reducing effects and not effects of alcohol on pain sensitization and hyperalgesia, which is more important for understanding the role of alcohol in chronic pain.

Recent work by Arout and colleagues (2016) used a novel intradermal capsaicin model to produce hyperalgesia within a double-blind placebo-controlled within-subjects design of two alcohol doses (BrAC=0.04 and BrAC=0.10) versus placebo among a small sample of healthy social drinkers (n=18). Results indicated that alcohol significantly attenuated the capsaicin-induced hyperalgesia, particularly in the high dose alcohol condition, with 30% reduction in hyperalgesia in the high alcohol condition and a 10% reduction in hyperalgesia in the low alcohol condition. Similarly, in a laboratory study of capsaicin-induced pain induction versus

placebo among a sample of hazardous drinkers (n=61), Moskal and colleagues (2018) found that individuals in the pain condition reported significantly greater urge to drink and greater intention to use alcohol. Results from both of these recent studies suggest that using alcohol to relieve chronic pain may be partially explained by alcohol's effect in reducing hyperalgesia and greater desire to drink when experiencing pain.

Emerging Studies on Neuroadaptations and Neural Circuitry in Humans

AUD and chronic pain share much of the same underlying neurocircuitry and both are complex disorders with heterogeneous and extensive impacts throughout the central nervous system (CNS). For example, the prefrontal cortex may serve to regulate cognitive, affective, and motivational aspects of both pain processing and alcohol consumption. However, stress and reward systems are also involved in modulating pain, experience of pain relief, and AUD. Numerous neurotransmitter systems have been implicated with shared genetic underpinnings likely influencing neural adaptations in both AUD and chronic pain. Yet, to our knowledge, no studies have examined the neural circuitry of chronic pain and AUD in human clinical samples and we could only identify two studies that examined neural correlates of substance use among chronic pain patients (Boissoneault et al., 2017, Petre et al., 2015). For discussion of the overlapping neural adaptations and circuitry we recommend prior reviews on the topic (Apkarian et al., 2013, Egli et al., 2012, Elman and Borsook, 2016, Yeung et al., 2017). The current review focuses on the few recent empirical studies that have examined potential neurobiological mechanisms of acute or chronic pain and alcohol or other drug use.

To test reward system involvement in the transition from acute pain to chronic pain (i.e., pain chronification) among smokers versus nonsmokers, Petre and colleagues (2015) conducted secondary data analyses from a longitudinal neuroimaging study of 68 individuals with subacute chronic back pain (duration of 4-12 weeks) who were followed for one year. Smoking was significantly associated with persistence of back pain at one year, and this effect was mediated by functional connectivity between the nucleus accumbens (NAc) and medial prefrontal cortex (mPFC) during a pain rating task. Specifically, smokers had significantly greater connectivity between the NAc and mPFC. Moreover, greater functional connectivity between the NAc and the mPFC predicted greater likelihood of pain persistence at the one-year follow-up. The investigators also found a reduction in functional connectivity of the NAc-mPFC among a small

group of patients (*n*=9) who quit smoking during the study. These results provide support for the hypothesis that corticostriatal circuitry is involved in the development of chronic pain and that individuals who engage in addictive behavior (smoking, in this case) may be at greater risk for chronic pain via greater coupling of the NAc and mPFC.

Boissoneault and colleagues (2017) examined associations between alcohol use and hippocampal volume among 40 women with fibromyalgia (45% of whom also had insomnia). Results indicated that any alcohol consumption over the 14 days prior to a magnetic resonance imaging (MRI) scan (average drinks/day less than one drink) was associated with significantly lower pain intensity and greater hippocampal volume, bilaterally, as compared to abstainers. Pain duration and total amount of alcohol consumption were not associated with hippocampal volume. Heavier drinkers and those with AUD were not included in the sample and, thus, it is impossible to know whether associations (or lack thereof) would be identified in an AUD sample. Given meta-analytic evidence of reduced hippocampal volume among individuals who engage in binge drinking and those with AUD (Wilson et al., 2017), it is potentially the case that some of the abstainers in the Boissoneault study were former heavy drinkers or that low levels of drinking may be protective among women with fibromyalgia.

Social Aspects of Pain in the Context of Alcohol in Humans

Alcohol intoxication may also inhibit neural responses associated with pain empathy, defined by neural reactions to viewing images of people experiencing a painful stimulus (e.g., knife about to cut into a hand, stubbing a toe on a board). Specifically, a double-blind placebo-controlled within-subjects study of 21 heavy social drinkers found that a 0.85 g/kg dose of alcohol, as compared to placebo, was associated with less activity in the dorsal ACC, right anterior insula, and right interior frontal gyrus during the pain image versus the no pain image (Hu et al., 2018). In addition, functional connectivity between the right anterior insula and fronto-parietal areas (including the dorsolateral prefrontal cortex) was increased while viewing pain images in the placebo condition, but not in the alcohol condition. These results suggest that acute alcohol administration may attenuate neural reactivity to viewing pain images among others and may have important implications for understanding how alcohol may dull pain responding, more generally.

Treatment Implications and Treatments Targeting Comorbid Chronic Pain and AUD

Pain is a significant risk factor for alcohol relapse during and following alcohol treatment (Witkiewitz et al., 2015). Pain reduction during alcohol treatment is associated with lower alcohol relapse risk (Jakubczyk et al., 2016), and heavier drinking is associated with greater pain severity, pain interference, and less pain coping among chronic pain patients receiving long term opioid therapy (Larance et al., 2016). Targeting the nexus of pain and alcohol use, as well as aberrant opioid use among patients prescribed opioid therapy (Landsman-Blumberg et al., 2017, Witkiewitz and Vowles, 2018), may be critical to improve treatment outcomes among individuals impacted by pain and AUD. Comorbidity is particularly concerning and important to target given that alcohol is commonly taken along with opioids and other substances among individuals experiencing chronic pain (Landsman-Blumberg et al., 2017, Larance et al., 2016, Novak et al., 2016, Vowles et al., 2018). Combined use of alcohol, opioids, and sedatives is particularly worrisome (Kelley et al., 2018, McCabe et al., 2006, Schepis et al., 2018, Votaw et al., 2019) given the increased risk for overdose from using these drugs in combination (Gudin et al., 2013, Jones et al., 2014).

Pharmacotherapy approaches that may be effective include those that target brain reward and stress systems. For example, there is preliminary evidence that naltrexone, a Food and Drug Administration approved medication for AUD, may be effective in the treatment of chronic pain (Patten et al., 2018) and extended-release naltrexone may be particularly useful in the treatment of co-occurring chronic pain, AUD, and opioid use disorder (OUD) (Hartung et al., 2014, Korthuis et al., 2017, Latif et al., 2019). However, individuals with OUD need to be fully detoxified prior to naltrexone treatment and compliance with naltrexone treatment is a major issue. There is preliminary data that acamprosate may be more effective for individuals who engage in drinking primarily to relieve negative affect (Roos et al., 2017) and it is unclear whether acamprosate may also be more effective for indivduals who are drinking to relieve negative affect mediated pain. Likewise, medications that are commonly used off-label for the treatment of AUD (Kranzler and Soyka, 2018), including gabapentin, selective serotonin and norepinephrine reuptake inhibitors, and topiramate are commonly used in the treatment of a variety of pain conditions (Ong et al., 2019, Silberstein, 2017). To date, no randomized clinical trials have systematically studied pharmacotherapy options for individuals with comorbid AUD

and chronic pain, and additional research is needed to test the efficacy of pharmacotherapy in this population.

Behavioral intervention approaches developed specifically for comorbid AUD and chronic pain are also lacking. However, there is promising preliminary data to support the efficacy of cognitive-behavioral treatment (CBT) for comorbid pain and substance use disorders (Barry et al., 2019, Morasco et al., 2016), although CBT has been shown to be modestly effective for AUD (Magill and Ray, 2009). Mindfulness- and acceptance-based interventions are effective for pain (McCracken and Vowles, 2014) and AUD (Bowen et al., 2014), and may be effective for the treatment of comorbid pain and AUD, particularly given recent evidence of effectiveness in the treatment of comorbid pain and OUD (Garland et al., 2014). Given the chronic and enduring nature of chronic pain, an acceptance-based approach that improves functioning and is less concerned with pain relief may be particularly important for individuals who have a history of using alcohol for pain relief. Noninvasive brain stimulation approaches, including transcranial magnetic stimulation and transcranial direct current stimulation, may also be promising tools given evidence of effectiveness for the treatment of pain (Ong et al., 2019) and AUD (Stein et al., 2018). Finally, physical exercise may be beneficial for improving health outcomes and quality of life among both chronic pain patients (Geneen et al., 2017) and individuals with AUD (Hallgren et al., 2017).

Future Directions for Research and Treatment of Comorbid Chronic Pain and AUD

Although the analgesic utility of alcohol has been well known for millennia, studies of the relationship between chronic pain and AUD in laboratory animals and humans remains in an incipient stage, and few satisfactory approaches are available for managing either of these devastating conditions. Despite the limitations of preclinical models, they have provided important new information about the biological basis of pain, AUD, as well as their interactions. Continued refinement of rodent models and improved insights into how chronic pain interacts with multiple physiological and psychiatric disease processes in humans will be necessary to propel future research discoveries (Figure 1). Motivational/affective components of pain need to be considered in both preclinical and clinical studies to further our understanding of pain, AUD, and their common comorbidity for the development of future treatment strategies. For example, it is important to expand preclinical and clinical models to consider pain interference, as an

important target for improving functioning and quality of life among individuals with AUD and chronic pain.

Bridging the preclinical and clinical models presented in this review, future research on chronic pain and AUD would benefit from in depth study of hypersensitivity and whether individuals with AUD and chronic pain experience analagesia or whether alcohol consumption causes greater hypersensitivity to pain among individuals with AUD and chronic pain. Similarly, the preclinical models examining neurobiological mechanisms of alcohol withdrawal-induced hyperalgesia are critical for informing our targets for alcohol relapse prevention among individuals with AUD and chronic pain during early abstinence from alcohol. Based on preclinical data (Dina et al., 2008), mifepristone could represent a promising medication for chronic pain patients with AUD, and several studies are currently underway to examine the effects of mifepristone in humans. Preclinical work on the analgesic effects of the endocannabinoid system (Zhang et al., 2014) would suggest that future work would also benefit from examining cannabis-based medications given some promising data in the areas of pain (Mücke et al., 2018) and AUD (Turna et al., 2019), although the potential harms of cannabis would need to be weighed against the potential benefits (Hall, 2001, Subbaraman and Kerr, 2019, Weinberger et al., 2016).

In conclusion, AUD and chronic pain are both complex and hetergenous conditions with high prevalence, high rates of comorbidity, and both produce devastating social, human, and economic costs. Preclinical and clinical research has only recently considered the comorbidity of AUD and chronic pain, and more research is needed to understand the mechanisms of chronic pain and AUD, and to develop treatment targets that might be effective in reducing suffering related to both pain and AUD. Future work focused on potential moderators of treatment effectiveness, such as sex/gender, genetic background, age, pain modality, and comorbid substance use (Ditre et al., 2019), is also critically important.

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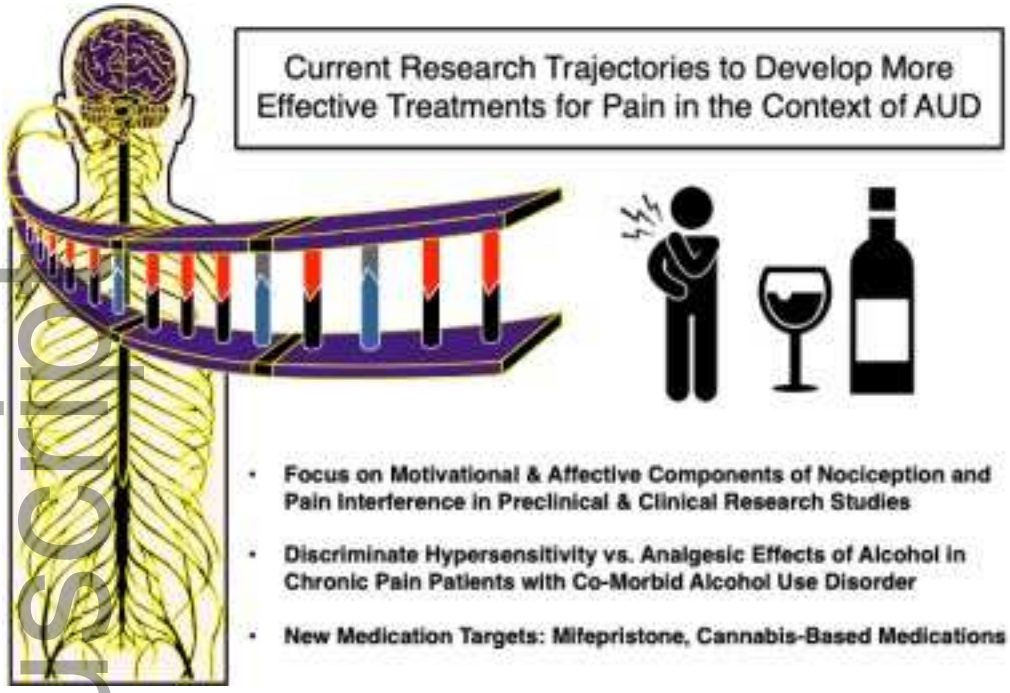

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