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From the Editors–Alcohol, Opioids, and Pain

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Opioids and alcohol are both effective analgesics under certain pain conditions. However, although the analgesic or pain-relieving properties of opioids are well known, information about the use of alcohol and its potential for misuse in the context of pain management has begun to emerge more recently. Alcohol doses required to alleviate pain are commensurate with binge drinking,[1] defined as drinking enough to achieve blood alcohol concentrations of 0.08 mg/dL or higher. Such pain-killing doses would typically occur after four drinks for women and five drinks for men in about 2 hours. Doses required for effective analgesia also are associated with unintentional injuries, violence, and traffic fatalities. Moreover, binge alcohol drinking over long periods to manage chronic pain also will foster profound negative health consequences, including organ damage and heightened cancer risk.[2]

After their initial pain-killing effects wear off, however, both alcohol and opioids, especially when used in high doses over long periods of time, can trigger opponent physiological responses that produce a temporary increase in pain sensitivity, known as hyperalgesia. These nociceptive processes reflect the unifying principle of homeostasis, the process by which complex physiological systems maintain biological stability. Simply put, what goes up must eventually come down to achieve a balanced resting state. With long-term heavy alcohol or opioid use, the opponent pro-nociceptive response grows, diminishing drug-induced analgesia (tolerance) while at the same time setting up a persistent sensory and emotional pain sensitization state that may occasion further drinking or opioid use, eventually heightening risk for the development of alcohol use disorder (AUD) or opioid use disorder (OUD) in vulnerable individuals. As such, understanding the AUD/OUD–pain relationship is among the most urgent public health challenges confronting us today.

Given the broad co-occurrence of hyperalgesia and AUD/OUD, pain may be best viewed as a core addiction phenotype. The view is supported by evidence acquired over the past decade that there is substantial overlap in brain circuitry and pathways underlying AUD, OUD, and pain centralization.[3] An improved understanding of the effects of alcohol on pain, the role of pain in alcohol misuse, and potential interactions between alcohol and opioids during pain treatment is an important step toward improved treatment outcomes for patients with chronic pain who are susceptible to AUD/OUD.

Pain is generally thought of as the unpleasant physical sensation following bodily harm or injury. Equally important, and mechanistically intertwined, is the psychological component of pain, particularly the emotional component of chronic and unrelieved pain. Mechanisms of neuroplasticity are thought

to underlie a "centralization of pain" at both spinal and supraspinal levels, and similar phenomena are used to describe how misused substances act on the brain to facilitate the development and maintenance of substance use disorder (SUD). In this topic series, Gilpin and colleagues describe functional changes in supraspinal circuits implicated in alcohol-induced changes in pain-related behavior ("Forebrain-Midbrain Circuits and Peptides in Hyperalgesia After Chronic Alcohol Exposure").[4] Their focus on interactions between midbrain and extended amygdala systems highlights novel avenues for managing pain in the context of AUD.

Alcohol or opioid misuse also can interact with pain to exacerbate negative emotional states (anhedonia, depression, and anxiety) as well as increase the sensitivity to such states (known as hyperkatifeia) to fuel continued or escalated substance use.[5] As with somatic pain, drinking alcohol or using opioids to cope with emotional pain only makes the situation worse. In their review, "The Convergent Neuroscience of Affective Pain and Substance Use Disorders," Pahng and Edwards describe contributions of stress-related signaling in key frontocortical brain areas to the dual and interactive manifestation of chronic pain and AUD/OUD symptomatology, highlighting research with refined animal models of these conditions.[6] In addition, economic and environmental sources of stress (such as social isolation and other anxieties associated with the COVID-19 pandemic) can further feed into this cycle, possibly contributing to increased alcohol drinking, opioid use, and suicide.[7] Within this theme, Zale and colleagues highlight transdiagnostic vulnerabilities in humans that are implicated across both maladaptive responses to pain (e.g., pain catastrophizing) and the motivation for alcohol and opioid use in their review, "Cognitive-Affective Transdiagnostic Factors Associated With Vulnerability to Alcohol and Prescription Opioid Use in the Context of Pain."[8]

Altogether, the reviews in this topic series represent the current state of neuroscience related to pain and AUD/OUD interactions spanning a wide range of research in both innovative animal models and humans. The translational efficacy of these directions will hinge largely on the continued collaborative efforts across health care professionals, multidisciplinary research laboratories, and National Institutes of Health institutes focused on these conditions. This topic series highlights many recent and exciting discoveries that will open up new conceptual avenues of research that may light the way ahead toward better treatment for both chronic pain and SUD.

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