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### **Novel Oxycodone Paradigm Highlights Mesocorticolimbic Mechanisms Underpinning Withdrawal-associated Behaviors with and without Chronic Pain**

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The development of physical dependence and addiction disorders due to misuse of opioid analgesics is a major concern with pain therapeutics. Our group developed a mouse model of oxycodone exposure to gain insight into molecular pathways in reward-related brain regions that are affected by prolonged exposure to oxycodone and subsequent withdrawal in the presence or absence of chronic neuropathic pain. RNA sequencing of medial the prefrontal cortex, nucleus accumbens (NAc), and ventral tegmental area revealed robust transcriptional responses to oxycodone withdrawal that were largely different between injured and uninjured animals. Upstream regulator analysis predicted an upregulation of histone deacetylase 1 (HDAC1) activity in several regions under withdrawal with and without pain. Direct inhibition of HDAC1 activity with RBC1HI, a novel HDAC1/2 inhibitor, alleviated sensory hypersensitivity and reduced affective deficits in animals under withdrawal and nerve injury. Our group is also pursuing addiction- and pain-related molecular candidates that work downstream of HDAC1 and are implicated in addiction and pain-like behaviors and synaptic plasticity, such as myocyte enhancer factor 2C (MEF2C). Preliminary data suggests that prolonged nerve injury may repress the expression/activity of MEF2C in the NAc. Viral overexpression of MEF2C in neurons of the NAc interrupts the maintenance of sensory hypersensitivity and anxiety-like behaviors in mice with prolonged nerve injury, as well as transcriptional and physiological maladaptations. Findings such as this are essential as they may lead to therapeutic strategies that can reduce the reliance of prescription opioids in chronic pain populations.