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Apremilast

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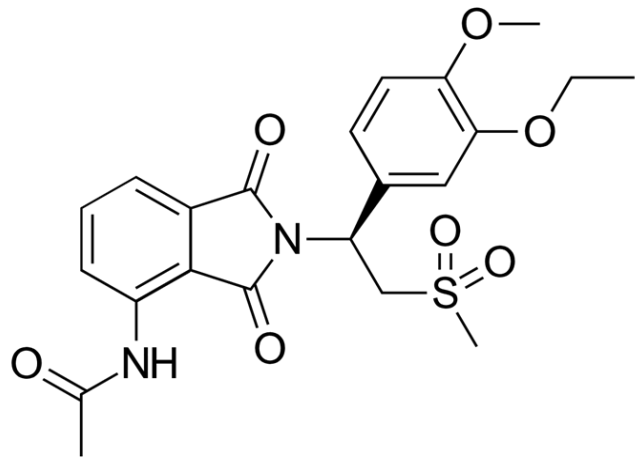
Researchers at Scripps Research have found in animal experiments that a medication already approved for inflammatory diseases could lessen both drinking behaviour and sensitivity to pain - two problems that often accompany alcohol use disorder. Findings indicate that apremilast, which is a phosphodiesterase 4 (PDE4) inhibitor that interferes with an inflammationrelated enzyme, might be repurposed to simultaneously curb alcohol consumption and relieve alcohol associated pain, making it a potential dualpurpose treatment for people with alcohol use disorder [1]. The chemical structure is presented in Figure 1.

Figure 1. Chemical structure of apremilast



Alcohol use disorder affects an estimated 400 million people aged 15 years or older, according to the World Health Organization. Chronic pain, although one of the most potent predictors of relapse, is rarely addressed in treatment plans. Many individuals with alcohol use disorder also experience mechanical allodynia, which is an extreme sensitivity where even light touch is painful, and this hypersensitivity often persists during abstinence, perpetuating further drinking and relapse [2,4].

Recent work has explored PDE4 as a molecular target involved in alcohol-related motivated behaviours. PDE4 enzymes break down cyclic adenosine monophosphate (a second messenger that regulates inflammatory signalling). Although PDE4 is most prevalent in immune cells, it is also widely expressed in the brain. Human genome-wide association studies have further linked PDE4 to alcohol use disorder [1].

Administering apremilast, a broad-spectrum PDE4 inhibitor approved by the United States Food and Drug Administration for psoriasis and psoriatic arthritis, has been shown to reduce alcohol consumption in both humans and animal models. Apremilast decreased binge-like drinking and self-administration progressive ratio breakpoints in mice bred for alcohol intoxication. Also, apremilast lowers the actionpotential threshold of medium spiny neurons in the nucleus accumbens that carry dopamine D1 receptors, while leaving those with D2 receptors unchanged [5,6].

Researchers evaluated apremilast in two sets of rats: one strain genetically inclined toward high alcohol consumption and another standard strain. Both groups had access to alcohol and were treated with either apremilast or a placebo. Apremilast markedly lowered alco-

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hol consumption across different genetic lines. It also reduced sensitivity to pain in most groups, not only immediately after drinking but also throughout abstinence, from a day after stopping alcohol to four weeks later. In additional experiments, apremilast increased inhibitory GABA signaling, which modulates pain and stress, in the central amygdala, a brain region involved in both addiction and pain processing. This increase appeared only in the standard rat strain, implying that the drug's effects on neural signaling may depend on genetic background or susceptibility to alcohol use disorder. Alcohol exposure elevated PDE4 gene expression in the brains of both male rat strains, reinforcing the connection between neuroinflammation, pain, and alcohol consumption [1].

Although other PDE4 inhibitors have been shown to reduce neuropathic pain in nonalcohol models, which is an effect linked to CAMP-mediated suppression of inflammatory signalling and reduced mechanical hypersensitivity, apremilast notably combines analgesic activity with reductions in alcohol consumption [7]. Because chronic pain is a major yet often neglected predictor of relapse in people with alcohol use disorder, this dual action could open the door to personalised treatments for individuals struggling with both AUD and pain [3]. However, robust clinical trials are needed to determine whether these benefits translate to humans. Future research should also investigate whether apremilast can alleviate the anxiety and other negative emotional states that frequently accompany alcohol withdrawal, potentially enhancing recovery prospects.

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