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Editorial

Therapeutic Potential of Psilocybin in Alcohol and Opioid Use Disorders: A Promising Role for Psychedelics

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Substance use disorder (SUD) remains a major challenge for healthcare systems world-wide. Based on the World Health Organization (WHO)'s most recent updated data, worldwide deaths related to alcohol consumption in 2019 was 2.6 million, accounting for 4.7% of all deaths, while deaths due to opioid use disorder (OUD) was 448,489 in the same year.[1] According to the Substance Abuse and Mental Health Services Administration (SAMHSA), 17.1% of people in the United States—approximately 48.5 million individuals—had a past-year SUD in 2023. Within this population, 28.9 million had alcohol use disorder (AUD) and 5.7 million had OUD. [2] There were more than 178,000 deaths from alcohol-related causes from 2020 to 2021 in the United States alone while 79,358 deaths were due to opioid overdose. [3,4]

Currently, the US Food and Drug Administration (FDA) has approved three medications for OUD: methadone, buprenorphine, and naltrexone.[5] Methadone has shown better outcomes at higher doses, which increases the risk of overdose.[6] Buprenorphine requires daily administration, while naltrexone must be administered after supervised medical withdrawal to avoid precipitating acute withdrawal. [5] FDA approved medications for AUD include disulfiram, acamprosate, and naltrexone. However, adverse effects and poor adherence have

limited disulfiram's efficacy. Acamprosate is approved for maintaining abstinence, and its effects are more pronounced when combined with psychotherapy. Naltrexone, while effective in reducing alcohol use, has only modest effects in decreasing relapse rates.[5] Given the limitations of existing treatments, there is a need to explore novel therapeutic options.

Classic psychedelics are compounds that alter emotions and perception by modulating the 5-hydroxytryptamine (5-HT) system.[7] Psilocybin is a naturally occurring psychedelic that was identified by Hoffmann from *Psilocybe Mexicana* mushrooms. Psilocybin is a prodrug which is converted to its active form psilocin by alkaline phosphatase.[7, 8] Psilocybin is considered one of the safest psychedelics and is well tolerated.[7, 8] Psilocin binds to various serotonin receptors, with the highest affinity at the serotonin 2A (5-HT_{2A}) receptor.[7] Although psilocybin is a Schedule I controlled substance in the US—indicating high abuse potential and no approved medical use—in 2018, the FDA designated psilocybin as a "Breakthrough Therapy" for treatment-resistant depression.[9] Consequently, clinical research on psilocybin for neuropsychiatric disorders has grown significantly.[10] In a randomized, double-blind trial involving cancer patients, two oral doses of psilocybin administered five weeks apart significantly reduced anxiety and depression, with effects persisting for at least six months.[11]

Over the past decade, interest in psilocybin for treating SUD has increased. In a proof-of-concept study with 10 volunteers and 36 weeks of follow-up, psilocybin combined with motivational enhancement therapy significantly reduced alcohol craving and increased abstinence.[12] A randomized clinical trial involving 95 participants by Bogenschutz et al. found that psilocybin administration was associated with reductions in both the percentage of heavy drinking days and mean daily alcohol consumption during a 32-week follow-up.[13] Another study examining psychological changes over 32 weeks in AUD patients showed that psilocybin improved self-awareness, increased self-compassion, and alleviated alcohol cravings and self-critical thoughts.[14] Additionally, psilocybin reduced neuroticism—likely through decreased depression and impulsiveness—and increased extraversion and openness in AUD patients, suggesting normalization of maladaptive personality traits.[15] A recent preclinical study reporting the effect of psilocybin on alcohol self-administration in male rats showed that psilocybin significantly attenuated ethanol intake by downregulating the rewarding effects of alcohol. [16] In a study by Alper et al., they showed that psilocybin has dose- and sex-dependent

effects on ethanol consumption. They also showed that a single dose of psilocybin decreased the consumption and preference for ethanol in male animals.[17]

The first study investigating the association between classic psychedelic use and opioid misuse was published in 2017. [18] This study analyzed the effects of psychedelics in a large population of opioid users between 2008-2013 and found that psychedelic use was associated with a 27% reduction in past-year opioid dependence and a 40% reduction in past-year opioid abuse. [18] In an online survey conducted by Garcia-Romeu et al., individuals with SUDs self-reported a reduction in drug consumption.[19] In a recent preliminary study of two patients with OUD stabilized on buprenorphine therapy, moderate-to-high doses of psilocybin combined with buprenorphine in conjunction with psychedelic-assisted therapy was well tolerated, with no serious adverse effects and minimal withdrawal symptoms or cravings. [20] Several ongoing clinical trials are currently evaluating the effects of psilocybin in patients with opioid dependence.[21-23] Preclinical studies in the OUD field are limited; however, recent studies have shown that psilocybin reduced morphine consumption in mice. [24] Furthermore, a study by Floris et al. (2025) investigated the effect of psilocybin on heroin seeking behavior in male rats, and the results indicated that psilocybin effectively inhibited heroin seeking and reduced relapse after forced abstinence.[25]

Some clinical studies have reported the effect of psilocybin on behavioral effects such as disruption of sleep after drug administration.[26, 27] However, Thomas et al. reported that psilocin slightly suppressed rapid eye movement (REM) sleep in the first hours after consumption in mice, but it did not have significant effects on long-term sleep-awake architecture.[28] Also, Fadahunsi et al. revealed that a single dose of psilocybin did not change eating behavior or decrease body weight in binge-like eating behavior and obesity models in animals.[29] Further studies are needed to characterize the effect of psilocybin on cognitive and adaptive behaviors.

In conclusion, psilocybin shows promise as a novel and effective therapeutic agent for the treatment of alcohol and opioid use disorders, particularly due to its long-lasting effects. However, it is important to emphasize that these benefits have been observed in conjunction with psychotherapy. Future research should focus on optimizing treatment protocols and conducting large-scale clinical trials to confirm psilocybin's efficacy in SUD populations.

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