

# Psilocybin as a potential treatment for nicotine dependence

## Introduction

Human beings have used, and possibly abused, mind-altering substances including nicotine and alcohol for at least 8,000 years (Fitzpatrick, 2015). The World Health Organization reports that 1.3 billion people smoke tobacco (WHO, 2009), which caused nearly half a million deaths in the United States and almost 6 million deaths globally each year (Jha et al., 2013; WHO, 2015).

Current treatment options for addictive disorders, while effective, still have high relapse rates in key disorders like alcohol and nicotine dependence (de Veen et al., 2017). Psychedelic therapies, including psilocybin, may offer therapeutic benefits for the treatment of SUDs. Psychedelics are also being explored for other mental health conditions including treatment-resistant depression, obsessive-compulsive disorder, Alzheimer's dementia, and alcoholism.

This chapter will briefly review the psychopharmacology and the evidence for psilocybin in addiction to nicotine.

## Psychopharmacology of psilocybin

Psilocybin (4-phosphoryloxy-N,N-dimethyltryptamine) is found in many species of Psilocybe fungi informally known as "magic mushrooms". It is chemically classified as a tryptamine and indolealkylamine (Passie et al., 2002b). Psilocybin is almost entirely transformed into the psychoactive serotonin analogue psilocin during first-pass metabolism (Tófoli & de Araujo, 2016). Minimum dosing is 10mg orally, with dose-dependent effects found with higher doses, and a duration of action of between 4 and 6 hours (Grob et al., 2011). Psilocybin is generally considered safe and well-tolerated based on human studies using intravenous doses of 1–2 mg and oral doses of 8–25 mg (Passie et al., 2002; Tylš, Páleníček, & Horáček, 2014), with low toxicity found in in vitro studies (Cerletti, 1958; Johnson et al., 2008).

There is strong evidence for low risk of toxicity, dependence and misuse of psilocybin in both newcomers and experienced users (Sessa, 2017), with magic mushrooms found to be the safest recreational drug (Winstock et al., 2017). Of particular note is that recreational psilocybin users report reduced psychological distress and suicidality (Hendricks et al., 2015).

Psilocin, like LSD, stimulates multiple serotonin (5-hydroxytryptamine) brain receptors (notably the 5HT<sub>2A</sub>, 5HT<sub>2C</sub>, and 5HT<sub>1C</sub> subtypes) which causes its neuropsychological effects (Halberstadt & Geyer, 2011). Psilocybin seems to carry a lower risk of negative emotional states than LSD (Grob et al., 2011). Further work found that psilocybin caused insignificant physical effects, with no change in ECG or temperature, and a short-lived benign increase in heart rate and blood pressure, which resolved after two hours (Hasler et al., 2004). Temporary alterations in endocrine hormones have been demonstrated after psychedelic use, specifically thyroid stimulating hormone, cortisol, and prolactin (Hollister & Sjöberg, 1964).

Despite this convincing safety data, there have been reports of both adverse effects and deaths associated with recreational psilocybin use (Borowiak, Ciechanowski, & Waloszczuk, 1998; Raff, Halloran, & Kjellstrand, 1992; Lim, Wasywich, & Ruygrok, 2012).

### Psilocybin and nicotine dependence

Currently approved pharmacotherapies for nicotine dependence include nicotine replacement therapies in various forms like gums, sprays, and patches; varenicline, bupropion, and cytisine. Despite improvements in affordable treatments for nicotine dependence including pharmacotherapy, support groups, and psychological therapies, the average smoker “quits” — and then relapses — some 30 times before successfully staying abstinent long-term (Chaiton et al., 2016). The relapse rate of conventional smoking cessation treatments is about 75% in the first week and 35% even after a year without smoking (Giulietti et al., 2020). Given the global extent and deleterious effects of smoking, and the difficulties people experience in trying to quit successfully, better treatments are urgently needed. Psychedelics in general, and psilocybin in particular, are of interest as potential therapeutics to support smoking cessation.

An online self-report study found a clear link between recreational psychedelic use and stopping smoking (Johnson et al., 2017). Nearly 40% of the anonymous respondents reported complete abstinence after taking a psychedelic drug; a further 28% revealed a substantial sustained reduction, and a further third noted a temporary reduction before returning to their old smoking habits. This suggests that 68% of people may reduce or abstain from tobacco after psychedelic use. Respondents also reported substantial reductions in anxiety and cravings. Those with higher rates of abstinence experienced stronger personal and spiritual significance during the psychedelic experience (Garcia-Romeu et al., 2014).

Based on these findings, a small Johns Hopkins pilot study of 15 patients explored the use of psilocybin to help heavy smokers quit (Johnson et al., 2014a). The subjects were chronic heavy smokers who had smoked nearly 2 packets of cigarettes daily for over 30 years on average. Subjects received two doses of psilocybin and frequent sessions of cognitive behavioural therapy. Both self-report questionnaires and biomarkers were used to confirm abstinence. This study demonstrated a remarkable 80% abstinence after 6 months follow up, which was maintained at 67% at 12 months, and 60% at 16 months (Johnson, Garcia-Romeu, & Griffiths, 2017). These rates are at least double the 35% quit success rate for the commonly used drug varenicline.

In this study, nearly 67% of subjects found that they had quit successfully by “changing how [they] prioritize values in life, so that reasons to smoke no longer outweighed reasons to quit,” and, “by strengthening your belief that you have the ability to quit and stay quit” (Johnson et al., 2014).

Based on these promising findings, a Phase II randomised controlled trial of psilocybin vs nicotine replacement therapy (NRT) as a control has started at Johns

Hopkins. It is currently recruiting up to 95 participants who will receive either NRT or a single high dose psilocybin session, with both also receiving a structured smoking cessation program. Subjects will have self-reported and biological measures of smoking cessation taken, and also Magnetic Resonance Imaging (MRI) scans to assess the neurological effects. It is scheduled for completion in 2022 (<https://clinicaltrials.gov/ct2/show/NCT01943994> ).

## Conclusions

While the evidence is still emerging, the psychedelic drug psilocybin appears safe and has therapeutic potential for treatment of nicotine dependence. Surveys of recreational users suggest an association between psychedelic use and long-term smoking cessation. A non-controlled pilot study of chronic heavy smokers found encouragingly high rates of short and longer-term smoking abstinence, superior to other available treatments. Research is ongoing comparing psilocybin to conventional treatment for nicotine dependence. If successful, and treatment is made available and affordable, the global health implications of reduced smoking are substantial.

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