James Marsh

Does psilocybin offer new prospects for tobacco cessation - new avenues or a pipe dream?

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James Marsh

Abstract

Tobacco smoking addiction is a problem yet to be solved. Frontline therapies, pharmacological or behavioural, are effective for some, but produce only moderate quit rates of around 30% at best. These therapies interact with, and interrupt, the cycle of addiction in a variation of ways, and the multifaceted approaches to cessation echo the complex nature of tobacco addiction as more than a nicotine dependence. Psilocybin, a $5\text{-HT}_{2A}\text{R}$ agonist, presents a possible new avenue for smoking cessation treatments. This is part of a new wave of psychedelic research shining light on potential therapeutic uses for psilocybin. A pilot study reported biochemically-verified cessation rates of 80%. The exact mechanisms through which psilocybin exerts action on addiction behaviours in not known. Hypotheses discussed suggest that psilocybin-occasioned mystical experiences and higher-level psychological processes are important, beyond the acute pharmacological effects. More research is needed to connect neurobiological understanding with the psychological effects. Optimism from promising results in studies of psychedelic therapies is tempered by the accompanying methodological biases, ethical uncertainties, and issues of practicality. Until more robust results can be demonstrated, and issues of legality and safety more adequately dealt with, psilocybin is likely to remain on the fringes of research and practice.

James Marsh

1. Introduction

Smoking caused over 10% of worldwide deaths in 2015, with a loss of nearly 150 million disability adjusted life years globally[1]. In the UK alone around 77,800 deaths were attributable to smoking, with smoking related ill health up 11% from ten years before[2]. Current frontline therapies for smoking cessation tackle both the pharmacological and behavioural sides of tobacco addiction. However, all present reasonably modest absolute quit rates, at 31.7% for combined NRT and <30% for other therapies[3]. As such there remains a population of smokers for whom there is a need for more effective interventions.

Encouraging results regarding the use of psychedelics in drug dependence came to the surface in the mid 20th century[4–7]. However, legislation[8] banning the use of psychedelics in the late 1960/70s put all significant research into psychedelic therapies on hold. This century has seen a small resurgence of research and clinical trials investigating the use and effects of psychedelics, such as psilocybin. Psilocybin, a $5\text{-HT}_{2A}\text{R}$ agonist[9], is a substance found in psilocybin-containing mushrooms, sometimes known as 'magic mushrooms' due to their hallucinogenic effects. A pilot study for the use of psilocybin as a smoking cessation intervention saw 80% quit rates in its participants[10].

I will illustrate the need to explore new addiction interventions through a case study of a patient, Stephen[*], who was the inspiration for this essay. I met Stephen during a GP placement at an inner-city practice, and was fortunate enough to have multiple follow-up appointments with him allowing me to explore his addiction experience and story. In addition, I will discuss the complex nature of tobacco addiction, and review the current basis of evidence for frontline smoking cessation interventions. I will outline the use of psilocybin in clinical studies in this century, discuss hypotheses surrounding its potential therapeutic mechanisms, and assess whether it offers genuinely novel treatments paths for tobacco smokers or is just a pipe dream.

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[*] Pseudonym used to maintain confidentiality.

2. Nature of nicotine addiction in smokers

A full review of the factors influencing tobacco addiction is beyond the scope of this essay. However, it is important to highlight briefly the complex nature of the addiction in order to understand how and why treatments for cessation work. It is widely understood that nicotine is the principal addictive component in tobacco smoking, with nicotine triggering clear molecular mechanisms[11]. Nicotine shares properties with other drugs of abuse, such as causing a dopamine overflow in the nucleus accumbens[12–14]. However, Balfour et al[15] highlight that: (1) evidence suggests some smokers find nicotine-free cigarettes to be just as satisfying[16], and (2) it is thought that nAChR are desensitised in long-term smokers, suggesting that the continual satisfying effects of smoking are mediated by factors other than a dopamine overflow[14,17–19]. It is reasonably suggested that other chemicals within tobacco smoke enhance the nicotine dependence, whilst association of sensory cues also plays an important role[15]. The smoking paraphernalia, immediate reward, and simple repetitive behaviour, contribute to a motor habit that is difficult to unlearn. The cycle of cue, craving, response, and reward is common to the lexicon of addiction research and popular science[20]. In Figure 1 this essay outlines diagrammatically how different frontline cessation interventions can interact with this cycle. Tobacco addiction is more than a simple nicotine dependence, with complex behavioural, psychosocial, and physiological factors[15].

2.1. Case Study – Stephen

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Stephen is a 63-year-old male who I first met during an appointment to discuss his COPD. His shortness of breath had been worsening recently, which was understandably concerning to him. He was an infrequent user of primary care services, so it was a relief that he was seeking care in this moment. He has no other medical history of note, or that he wished to disclose. Stephen is a retired construction worker, lives alone in housing provided by the council, and has a 50 pack-year smoking history.

Towards the end of the initial appointment, the GP that I was shadowing asked about his attempts to quit smoking, to which Stephen reported that he had given up on his latest attempt due to stress. He kindly agreed to come back in for have an appointment with myself to chat about his smoking history and previous attempts to quit.

Stephen started smoking as a teenager, but for decades never felt that it was an issue, assuming he could quit if he wanted to. Working in construction, for most of his life he viewed smoking as a great social tool, and stress reliever. He has made 5 previous attempts to quit over the last 15 years, utilising approaches from group therapy to NRT and Bupropion. We discussed his thoughts on why those attempts hadn't been successful. Stephen disclosed that each time he tried, he would have a month or two of improvement but that there was always another inevitable stressor around the corner that would lead to him taking up smoking again. He noted to me that there are more harmful substances he could be turning to, which, whilst a fair point, underlined that fundamentally Stephen felt he needed something at least to help him through the stresses of modern life. I hesitate to put words into Stephen's mouth, but at the heart of it, it seemed that he didn't believe that quitting long term was really ever possible, if even desirable at this stage in his life.

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Meeting with Stephen multiple time across a two months period, I was grateful for his honesty and frank approach, and would love to have been able to share more than a summary of his story. My time with Stephen led me to look beyond what might be considered the standard approaches, into more novel approaches to tobacco cessation.

3. Tobacco Cessation

Tobacco smoking interventions cover a range of objectives. Interventions on a population level seek to affect public perception, and as such decrease the prevalence and uptake in society, through policy[21], education[22], or advertising[23,24]. Some interventions focus on reducing harm in people who continue to smoke tobacco[25]. Whilst these are both important interventions for reducing the burden of tobacco smoking on individuals and society, they lie outside the focus of this essay (individual

cessation). This section will discuss interventions which focus on helping individuals quit tobacco smoking.

3.1. Pharmacological interventions

Direct comparison of quit rates between the different types of intervention is difficult, due to the variation between trials in follow-up period, additional support provided, and treatment of control arm.

3.1.1. Nicotine replacement therapy (NRT)

NRT is the most widely used pharmacological agent for smoking cessation. This is perhaps unsurprising, given it is relatively inexpensive, can be obtained easily over the counter, and can be utilised through multiple different methods. NRT includes gum, transdermal patches, oral and inhaled preparations, and intranasal spray, all of which confer a significant increase in the chance of quitting successfully when compared with a placebo (RR 1.55 (95% CI: 1.49-1.61), from 133 RCTs, including 64,640
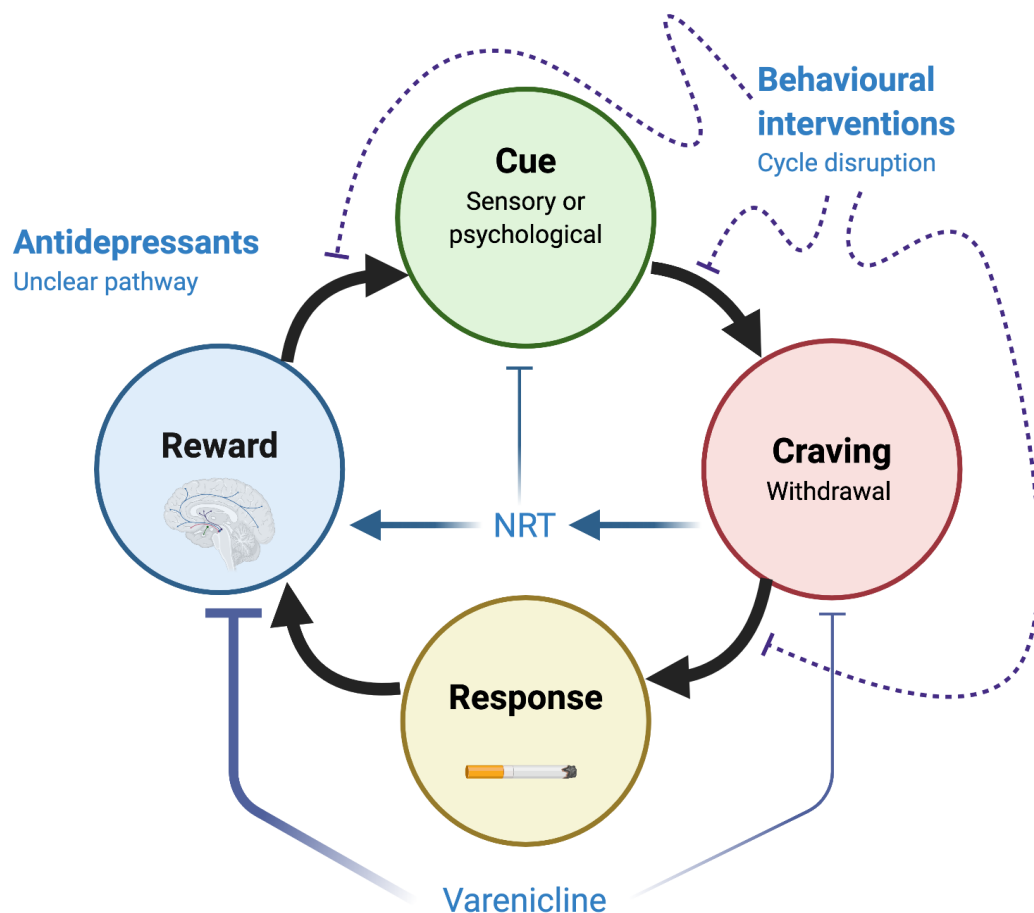

Figure 1. The effects of frontline cessation therapies on the addictive cycle of tobacco smoking. The cycle structure is adapted from[20].

participants)[26]. It was concluded that the relative beneficial impacts of NRT were independent of the level of additional support provided[26].

A systematic review of 63 studies comparing types of NRT with each other showed that was a 15%-36% improvement in quit rates when a nicotine patch is used alongside one additional form of NRT[27]. This is likely to be attributable to the ability of the combined treatment to provide constant low levels of nicotine from slow release patches, as well as shorter bursts of high levels of nicotine from a lozenge or spray. Most studies of NRT have a final follow-up point of 6-12 months after treatment begins. However, the ultimate goal of cessation interventions is life-time abstinence, and as such, studies with time-frames up to 1 year fail to give an accurate picture of efficacy. NRT studies with a 6-12 month follow-up overestimate the long-term benefit and cost-efficacy of NRT by around 30%[28]. A meta-analysis of long-term (2-8 years) cessation in NRT studies concluded that the majority of relapses after 12 months occurred within the 1st and 2nd year, suggesting that NRT does therefore have some long-term effect on smoking cessation.

NRTs are certainly a clinically valuable treatment in achieving smoking cessation. However, they have a rather modest ambition, as they do not break the addictive cycle as much as simply providing a smoke-free way to continue it (Figure 1).

3.1.2. Nicotine receptor partial agonists

Nicotine receptor partial agonists work to attenuate the addictive nature of nicotine. These drugs are partial agonists to $\alpha_2\beta_4$ nAChR. They maintain moderate dopamine levels (agonist) to minimise withdrawal symptoms, whilst also reducing smoking satisfaction (antagonist), this is laid out diagrammatically in Figure 1. Varenicline and Cytisine both have evidence of effective use.

Two double-blind RCTs comparing Cytisine with placebo[29,30], including 937 participants, delivered a combined RR of 3.98 (95% CI: 2.01-7.87) for biochemically verified abstinence at 6-12 months[31]. A open-label 2014 study[32] of Cytisine versus NRT showed a benefit of Cytisine over NRT with an RR of 1.43 (95% CI: 1.13-1.80). The open-label nature of this study suggests more research is needed.

The most widely used nicotine partial receptor agonist is Varenicline. Evidence suggests Varenicline is superior to any other single form intervention[33]. A systematic review of 39 trials, involving over 25,000 participants, synthesised results comparing Varenicline to either placebo, bupropion, or NRT[31]. For Varenicline versus placebo, the pooled RR for abstinence is 2.24 (95% CI: 2.06-2.43)[31]. The number needed to treat for an additional beneficial outcome (NNTB) highlights the results for comparison of Varenicline versus bupropion/NRT. Estimating a control quit rate of 7.5%[31], the NNTB for Varenicline is 11 (95% CI: 9-13), 23 (95% CI: 20-25) for NRT, and 22 (95% CI: 18-28) for bupropion. Whilst there remains little uncertainty as to the efficacy of Varenicline, there exists a continuing debate over the connection between Varenicline and the occurrence of neuropsychiatric serious adverse events (SAEs)[31].

3.1.3. Antidepressants

Bupropion has dopaminergic and adrenergic actions, and appears to be an antagonist of nAChR[34,35]. Nortriptyline, a TCA, increases serotonergic and noradrenergic activity by inhibiting their reuptake[34]. A 2020 systematic review of their use in smoking cessation highlighted high-certainty evidence that bupropion increased long-term cessation rates (RR 1.64 (95% CI: 1.52 to 1.77))[36]. Psychiatric adverse events (AEs) were more commonly reported amongst participants randomized to bupropion. Six studies comparing nortriptyline with placebo, found an RR of 2.03 (95% CI: 1.48 to 2.78) in favour of nortriptyline[36]. The mechanism through which they affect cessation is not well understood. These antidepressants interact with receptors important in nicotine addiction[37], and they may also work through alleviating depressive symptoms associated with withdrawal.

3.2. Behavioural and psychological interventions

The use of behavioural interventions for smoking cessation, highlights the complex nature of smoking addiction. Behavioural interventions disrupt, and facilitate unlearning of, the habitual cycle through minimising cues, increasing motivation, and imposing practical barriers (Figure 1). There exists a range of behavioural therapies including telephone counselling[38], motivational interviewing[39], physician advice[40], group-therapy[41], or messaging-based interventions[42]. There is a strong body of evidence for the use of combined pharmacotherapy and behavioural treatment over

less intensive support[43]. Increasing the intensity of behavioural support offered increases the chance of success by 10-20%[44].

4. Psilocybin

Given the limitations illustrated by these low success rates, there is interest in dramatically new ways to approach tobacco cessation.

4.1. History

Psilocybin is part of a larger family of drugs known as psychedelics. Psychedelics such as psilocybin and LSD are serotonin receptor (predominantly 5-HT$_{2A}$R) agonists[9], and can alter consciousness in a marked fashion. From the early 1950s, several studies on psychedelics, namely LSD, suggested potential uses in the treatment of OCD, substance dependence, and in the terminally ill[45–48], with specifically promising results for the treatment of alcohol dependence[4–7]. These studies lacked the rigorous control expected in modern medicine, meaning optimism from their results is rightly tempered. That said, a recent meta-analysis of RCTs conducted during that time found that LSD-facilitated treatment of alcoholism approximately doubled the success rates at first follow-up[49]. Advances in psychedelic research were significantly hindered from the mid-1960s onwards due to legal restrictions, and controversy around the recreational use of psychedelics. In 1971 psilocybin was classed as a Schedule 1 drug[8].

4.2. New avenues

This century has seen a revival of sorts in psychedelic research. A more grounded understanding of the pharmacology, psychology, and neuroimaging has provided a foundation for a small number of clinical trials, the majority of which have studied psilocybin. Due to study limitations, most of these trials are regarded as safety and tolerability trials. Consistently positive outcomes have been reported for the use of psilocybin for treating OCD[50], psychological distress in terminal cancer patients[51–53], depression and anxiety[54], and alcohol[55] and tobacco[10] addiction (Table 1). Participants are usually given a 0.3-0.4mg/kg dose of psilocybin in a supervised and assisted session. In the study from Johnson et al[10] quit rates were reported of 80% at 6-months, and 75% (9/12) at long-term follow-up (average 2.5 years)[56]. These results far exceed the quit rates seen from any of the interventions discussed earlier.

Study	Study focus	Sample size	Study structure	Main outcome
Moreno et al (2006)[50]	Obsessive compulsive disorder (OCD)	n=9	Single arm, up to four doses.	Improvements seen within 24hrs – not dosage dependent
Grob et al (2011)[51]	Anxiety in patients with advanced-stage cancer	n=12	RCT, double blind, crossover, inert placebo. Single dose.	Significant decrease in trait anxiety at 3 months and depression at 6 months
Johnson et al (2014)[10,56]	Tobacco dependence	n=15	Open-label. Four CBT sessions, up to three doses.	80% of sample abstinent at 6 months (67% at 12 months).
Bogenschutz et al (2015)[55]	Alcohol dependence	n=10	Open-label. Up to two doses after 7 motivational therapy sessions.	Significant reduction in drinking behaviours for up to 9 months.
Carhart-Harris et al. (2016)[54,57]	Treatment-resistant depression	n=12 (20 after study extension)	Open-label. Two doses.	Significant reduction is depressive symptoms for up to 6 months.
Ross et al. (2016)[52]	Anxiety and depression in patients with life	n=29	RCT, double-blind, crossover, placebo=niacin. Single dose.	Sustained decrease in symptoms vs niacin (pre-

	threatening cancer			crossover), and sustained for 6.5 months.
Griffiths et al (2016)[53]	Anxiety and depression in patients with life threatening cancer	n=50	RCT, double blind, crossover, placebo=very lose dose psilocybin. Single dose.	Sustained decrease in symptoms vs placebo (pre-crossover), and sustained for 6 months.

Table 1: Overview of clinical trials investigating therapeutic uses of psilocybin.

Johnson et al[10] suggest that higher-order psychological mechanism may be important to psilocybin's effect. They highlight common themes in participant responses as 'increased temporal horizon, increased self-efficacy, and altered life priorities'[10]. Participants who were abstinent at 6-month follow-up scored significantly higher, on a measure of mystical-type experience resulting from psilocybin, than those who had relapsed[58]. On long-term follow-up[56], 86.7% of participants rated their psilocybin experience as one of the five most 'personally meaningful and spiritually significant experiences in their lives'. This is consistent with (1) evidence that psilocybin occasions 'mystical-type experiences' with 'sustained personal meaning' in healthy volunteers[59], where at 14-month follow-up, 61% of participants linked their experiences with positive behavioural change[60], and (2) increased spirituality is associated with positive outcomes in substance abuse recovery[61–64]. Figure 2 (below) illustrates how these effects may disrupt the addictive cycle.

Issues highlighted in this study[10] are common to many in Table 1. Small sample population (n=15) and an open-label trial means that one cannot draw any definitive conclusions about psilocybin's role. All psilocybin clinical trials, except two[52,53], have been conducted in an open-label format. When blinding is used, it is worth questioning the extent to which it can ever been achieved with such an experiential treatment[65], and whether or not blinding it this scenario is even be desirable. The robustness of evidence is a barrier yet to be overcome when comparing psilocybin which other

smoking cessation treatments. Emotionally excitable states in volunteers immediately before psilocybin intake is linked with increased likelihood of mystical-type experiences[66]. The generalised efficacy of such trials is put into question, considering participants are selected on the basis of a willingness to engage with psychedelic research.

Johnson et al[10] provided participants with significantly more behavioural support that most smoking cessation studies. Participants reported that the sense of momentum once engaged with the study aided quitting[67]. Whilst this will likely have affected results, it is unlikely to have been the cause of such marked improvements in quit rates, when these rates are not seen in other RCTs of CBT programmes[68]. Most
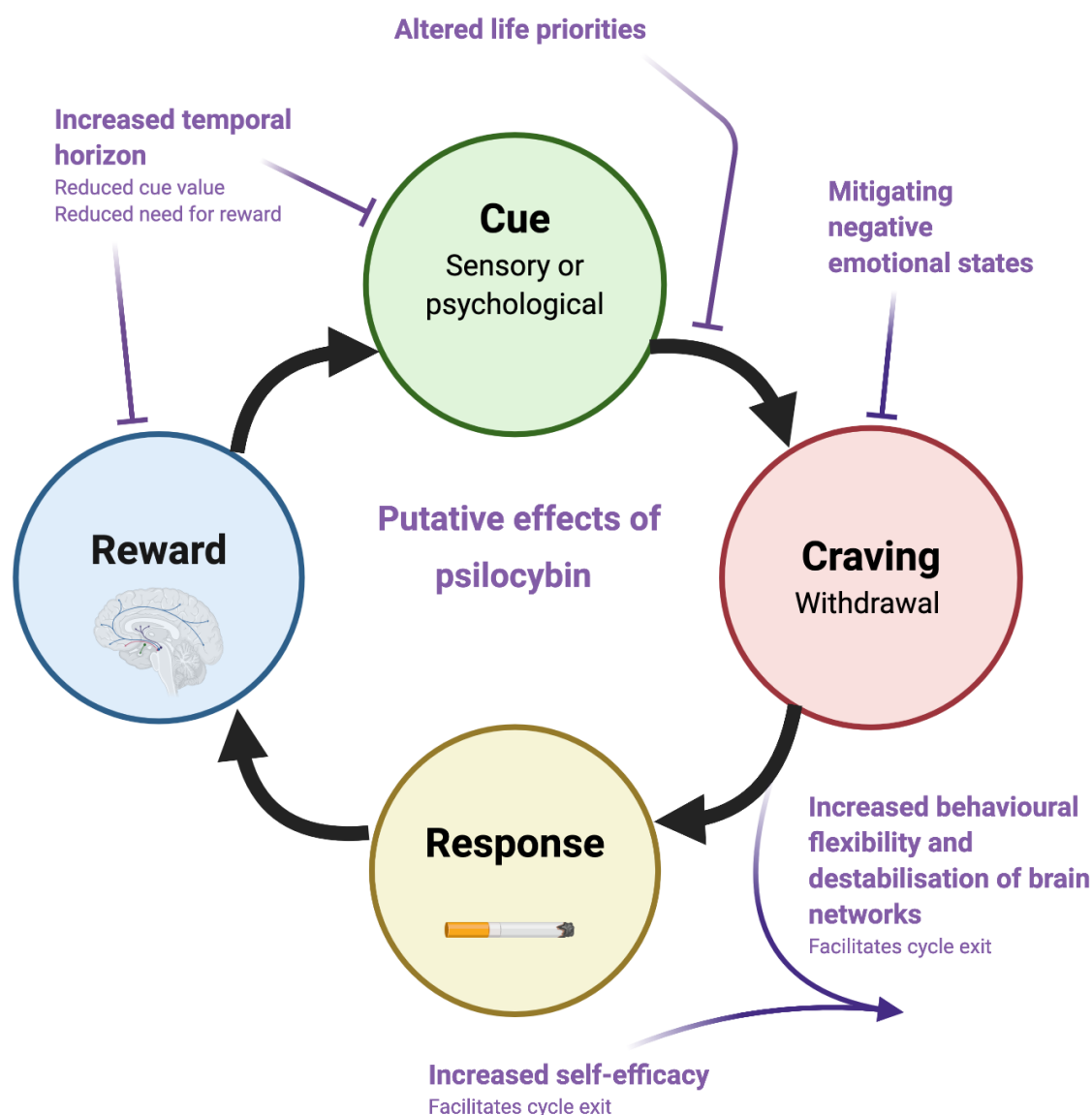

Figure 2. How the putative effects of psilocybin might interact with the cycle of addiction.

research with psilocybin is keen to defend the safety of its use – perhaps this is unsurprising given the politically charged historical narratives around the use of psychedelics. Johnson et al[10] report AEs such as increased BP, HR, headaches and dysphoric subjective effects. However, these effects are limited to the study session time, and as such can be managed within the context of the supervised session. AEs stemming from other pharmacotherapies can be persisting in nature, as they require repeated administration.

Whilst studies on the effect of psilocybin on addiction are relatively limited in design and definitive conclusions, results are certainly encouraging enough to warrant further exploration and RCTs[69].

4.3. Potential mechanisms

Whilst it is clear that psilocybin has a significant pharmacological effect on the brain, it differs from standard pharmacotherapies, as its effects endure beyond its metabolic half-life[70,71]. This is echoed by a qualitative analysis of the accounts of participants in the Johnson et al study[10], highlighting that 'experiences of interconnectedness, awe, and curiosity' were present long after the acute effects[67].

The structure of psilocybin is similar to 5-HT (serotonin), and binds with high affinity to 5-HT receptors in the brain (mainly 5-HT$_{2A}$R)[9,72]. De Veen et al[73] suggest two potential mechanisms by which psilocybin could exert an influence on substance use behaviours. They highlight the role of 5-HT$_{2A}$ and 5-HT$_{1A}$ receptors in two areas. Firstly, in cognitive inflexibility and compulsivity – hypothesising that 5-HT$_{2A}$R agonism may increase behavioural flexibility through decreased salience network (SN) and increased executive control network (ECN) activity. Secondly, that agonism of 5-HT$_{2A}$R and 5-HT$_{1A}$R increases serotonin and cortisol levels[73], which mitigate negative emotional states and activate larger-scale brain networks respectively[74]. Studies using fMRI have shown that psilocybin administration acutely alters brain network activity, specifically decreasing connectivity within the default mode network (DMN)[75]. The DMN, as well as the SN and ECN, are thought to play key roles in substance use disorders[76–78].

One hypothesis connects the destabilisation of larger scale brain-networks with behavioural flexibility[79], suggesting that an acute destabilisation permits the altering of brain networks beyond the timeframe of the acute effects. This facilitates both relearning and exit from the addictive cycle (Figure 2). It is noted[69] that this hypothesis also accounts for the importance of the context and accompanying psychotherapy that are thought to have a key role[80]. A hypothesised action through mitigation of negative emotional states[73] may function through minimising affective withdrawal symptoms (Figure 2). This is reinforced by evidence from depression studies[52–54], together with an online survey[81] conducted by Johnson et al of 358 participants who reported tobacco cessation associated with psychedelic use. There were consistent reports across all groups of less severe affective withdrawal symptoms (e.g. depression, cravings) after psychedelic use, when compared to previous quit attempts[81].

The broad spectrum of action of psilocybin on higher-level function may be a key factor in tackling the complex nature of tobacco dependence. Further research is needed to test mechanistic hypotheses.

4.4. A pipe dream

Goodwin[65] calls for an 'upbeat pessimism' when assessing the evidence of current psychedelic studies.

Hallucinogenic substances have the potential to illicit psychotic episodes[80,82]. Whilst these may be rare in healthy individuals, they highlight that controlled environments and proper safety guidelines are necessary for any advancement in research. SAEs can usually be prevented by screening, expert guidance, controlled administration environments, and pre-exposure education[80]. If there is to be safe advancement, it is key to identify methods by which at risk individuals can be screened and managed. Evidence suggests the risk of addiction to psilocybin is low[80,83]. However, there exists a very real abuse potential, and authors involved in some of the studies in Table 1 have appreciated the appropriateness of CSA scheduling, should psilocybin be licensed for medicinal use[84].

Practically speaking, psilocybin-assisted tobacco cessation requires costly, intensive, supervised treatment regimes. Unless its financial efficacy as a treatment can be more robustly demonstrated, it seems it will be confined to the fringes of the plausible options at best. Furthermore, some patients may be unwilling to engage with such 'mind manifesting' therapies, even if their efficacy is more robustly concluded. Much of the research conducted around psilocybin is by a small handful of researchers. Whilst not a basis on which to doubt the merits of such research, it suggests that the medicinal use of psychedelics is far from becoming widely adopted at this present time. Furthermore, there remains a question over the political and legal status of psilocybin as a medicine.

5. Conclusion

NRT, Varenicline, and bupropion, alongside behavioural interventions, remain the best options for smoking cessation. However, there remains of population of smokers for whom current treatment has not proven to be effective. Psilocybin presents a possible new avenue in both smoking cessation treatments and further afield. This new avenue requires significantly more exploration, and the current basis of evidence provides at very least a foundation for such research. However, there are many unanswered questions, and further research needs to build on current neurobiological understanding to establish mechanisms through which psilocybin might be effective (both in tobacco dependence and more widely). It must also seek to outline structures through which more robust psychedelic trials can be conducted, without which the current body of evidence is unlikely to grow in the certainty of its conclusions, which is vital for influencing clinical practice and academic discourse. For now, psilocybin research is likely to continue to operate on the fringes of medical research, and the mainstream use of psilocybin as a smoking cessation treatment remains a pipe dream that may or may not one day become a reality.

James Marsh

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