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REVIEW

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## Psilocybin for treating substance use disorders?

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### ABSTRACT

**Introduction:** Evidence based treatment for Substance use disorders (SUD) includes psychotherapy and pharmacotherapy. However, these are only partially effective. Hallucinogens, such as psilocybin, may represent potential new treatment options for SUD. This review provides a summary of (human) studies on the putative therapeutic effects of psilocybin, and discusses the receptor systems, brain regions and cognitive and emotional processes mediating psilocybin's effects. Psilocybin's chemical structure is similar to that of serotonin. Dysregulations in the serotonin system are associated with alterations in stress hormones, such as cortisol, and mood disorders. After psilocybin administration cortisol levels spike and activate the executive control network, with subsequent increased control over emotional processes, and relief of negative thinking and persistent negative emotions. Preliminary data of ongoing alcohol and smoking addiction studies in humans shows promising effects of psilocybin administration on substance use. Importantly, psilocybin has a low risk of toxicity and dependence and can be used safely under controlled clinical conditions.

**Areas covered:** This paper is a narrative review based on the search terms: psilocybin, substance use disorder, addiction, depression, serotonin. Literature on potential efficacy and mechanisms of action of psilocybin in SUD is discussed.

**Expert commentary:** Recent positive findings with psilocybin need confirmation in well-designed placebo controlled randomized trials employing a large sample size.

### ARTICLE HISTORY

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### 1. Rational and outline of this review

Substance use disorders (SUDs) are common, but current pharmacotherapies have only limited success in treating SUDs. Moreover, medication reducing craving and substance use is mainly available for alcohol dependence and to a lesser extent for other substances. Hallucinogens (like lysergic acid diethylamide [LSD] and psilocybin) may be a group of agents with potential anti-craving properties and subsequently reducing substance use in SUD patients. For instance, LSD and psilocybin have previously been shown to effectively alleviate symptoms of alcohol and nicotine dependence. However, due to the long plasma half-life (14 h) during which participants need to be closely supervised, this hallucinogenic drug has a limited potential in the treatment of SUD. A number of recent studies have shown therapeutic potential of another hallucinogen called psilocybin in the treatment of SUD, which has a substantially shorter plasma half-life (6 h). In this review, we provide a summary of (human) studies in which the putative therapeutic effects of LSD and psilocybin have been tested. In addition, we shortly discuss the receptor systems, brain regions, and cognitive and emotional processes that may mediate psilocybin's mode of action. Both beneficial and potentially harmful effects of psilocybin will be discussed.

### 2. Introduction

For centuries, substance use and SUD have been rather common. According to the World Health Organization global burden of disease study, about 11.8 million people are suffering from illicit drug dependence worldwide [1]. Several factors contribute to the risk of developing SUD, including socioeconomic factors, like lifestyle, life events, adverse life events (both during childhood and current), drug availability or cultural acceptance to use drugs, and psychiatric disorders such as depression, bipolar disorder, anxiety disorders, and/or schizophrenia [2].

Treatment of SUD often involves both psychological and pharmacological interventions, such as cognitive behavioral therapy, motivational interviewing, family therapy, and certain medications. Despite increasing effectiveness of SUD treatment, still about 50–60% of patients with drug and alcohol use disorders relapse within 6–12 months after treatment [3]. New treatments preferably focusing on reducing craving and subsequent substance use are therefore urgently needed. The hallucinogen psilocybin may provide a new treatment option for SUD patients, given the beneficial results observed in recent studies (for references, see below).

## 2.1. SUDs

The fifth edition of the Diagnostic and Statistical Manual of Mental Disorders (DSM-5) [4] provides 11 criteria (see Box 1) for SUD, with a minimum of two required during a 1-year period in order to meet the criteria for an SUD. SUDs are defined as chronic disorders of brain reward, motivation, and memory processes that have gone awry [4]. Activation of the brain's reward system may be central to the development of SUD. This has been shown by many studies and has been nicely reviewed by Volkow and Li [5]. Below, we shortly outline the main mechanisms found to be involved in SUD.

### 2.1.1. Monoamines and SUD

The neurobiology of SUD is complex and involves multiple neurotransmitter systems including the dopamine (DA), serotonin [5-hydroxytryptamine (5-HT)], and corticotropin releasing factor (CRF) stress systems. All substances of abuse have in common that they increase DA release in the striatum, and thereby mediate reward [5]. The underlying mechanisms are, however, dependent on the pharmacological profile of the drug. The psychostimulant cocaine for example inhibits DA, noradrenaline, and serotonin reuptake transporters (SERTs) and thereby increases synaptic levels of these monoamines. The amphetamine-type stimulants cause the release of monoamine by reversing monoamine transporter function [5]. Stress system CRF receptors are found in both the dorsal raphe nucleus (DRN) and the ventral tegmental area (VTA), brainstem areas where serotonergic and dopaminergic cell bodies are located, respectively [5]. This allows a strong interaction between the brain stress systems and the monoamine neurocircuitries involved in SUD, including DA and 5-HT. This review only includes a selection of neuropharmacological findings related to the DA, 5-HT, and CRF systems, namely those that are targeted by psilocybin. Other potential neuropharmacological mechanisms of action of psilocybin are beyond the scope of this paper.

**Box 1.** The DSM-5 includes 11 criteria for the assessment of substance use disorders (SUD). A minimum of two criteria is required to meet the criteria of SUD. The total number of criteria someone meets determines the severity of the SUD. Two or three symptoms indicate a mild SUD, four or five symptoms indicate a moderate SUD, and six or more symptoms indicate a severe SUD.

1. Taking the substance in larger amounts or for longer than meant to
2. Wanting to cut down or stop using the substance but not managing to do so
3. Spending a lot of time getting, using, or recovering from use of the substance
4. Cravings and urges to use the substance
5. Not managing to do what you should at work, home, or school, because of substance use
6. Continuing to use, even when it causes problems in relationships
7. Giving up important social, occupational, or recreational activities because of substance use
8. Using substances again and again, even when it puts you in danger
9. Continuing to use, even when you know you have a physical or psychological problem that could have been caused or made worse by the substance
10. Needing more of the substance to get the effect you want (tolerance)
11. Development of withdrawal symptoms, which can be relieved by taking more of the substance

**2.1.1.1. DA in SUDs.** The reward system is at the basis of normal learning and decision-making through positive reinforcement by DA release [5]. While substances of abuse initially elicit a massive increase in extracellular DA, long-term excessive substance use has been proposed to be related with reduced sensitivity of dopamine D2 receptors, possibly resulting from downregulation of dopamine D2 receptors [5]. It has been suggested that this DA hypofunction in the brain triggers a strong motivation to continue drug use as an attempt to re-experience the positive reinforcement as experienced during initial drug use (positive reinforcement). The DA system also plays a role in emotional processes. For instance, depression has been associated with a reward deficit [6]. This overlap in DA dysfunction may potentially explain the high comorbidity between SUD and amongst others, depression [7].

**2.1.1.2. Serotonin in SUDs.** DA release in the reward system is strongly modulated by 5-HT receptors (specifically 5-HT<sub>2A</sub> and 5-HT<sub>2C</sub> receptors) [8]. Indeed, multiple studies manipulating central 5-HT levels have reported effects on reward processing (for review, see Cools et al. [9]). Additionally, as reviewed by Muller and Homberg [10], a 5-HT deficit occurring upon chronic cocaine exposure may be associated with increased impulsivity, which also feeds addictive behaviors. Furthermore, it has been demonstrated that stimulation of serotonergic DRN afferents to the nucleus accumbens abolishes cocaine reward and diminishes depressive-like behaviors in animals [11]. These findings suggest that 5-HT-mediated changes in emotion can affect addiction-related disturbances in the reward neurocircuitry.

### 2.1.2. Neuropeptides and SUDs

Next to the monoamine neurotransmitter systems, neuropeptides (like CRF) are also significantly involved in SUD, as reviewed by Koob [12]. CRF is released from the paraventricular nucleus (PVN) of the hypothalamus and drives the hypothalamus–pituitary–adrenal axis (HPA-axis). CRF stimulates the release of adrenocorticotrophic hormone (ACTH) in the blood which in turn stimulates the secretion of cortisol by the adrenal cortex. The HPA-axis contains a negative feedback mechanism, which allows cortisol – through binding at glucocorticoid receptors in the hippocampus and prefrontal cortex – to reduce CRF release by the PVN, and subsequently to reduce adrenal secretion of cortisol.

The HPA-axis plays an important role in substance use. Animal studies have demonstrated that removal of the adrenal axis hinders the acquisition of drug self-administration, suggesting that cortisol (corticosterone in animals) is needed for the initial behavioral response to drugs. It has been thought that cortisol/corticosterone signals arousal and also exerts rewarding effects involved in the initial acquisition of drug use behavior [13].

The HPA-axis has also been shown to be relevant in the maintenance phase of drug self-administration in animals, through changes in higher order emotional regions like amygdala, where CRF is abundantly expressed [14]. It has been demonstrated that repeated activation of the dopaminergic VTA (by substance use) and stimulation of DA receptors in the amygdala activate the CRF system in the amygdala [15].

Furthermore, there are tight interactions between the 5-HT and CRF systems at various levels. For instance, it has been reported that a cluster of serotonergic neurons in the DRN expresses CRF and that these neurons project to CRFergic neurons in the central nucleus of the amygdala [16]. Furthermore, rats lacking SERT display high basal corticosterone levels in blood plasma [17] as well as reduced cocaine-induced 5-HT release [18], and increased compulsive cocaine self-administration [19,20] compared to wild-type animals. It has been suggested that the CRF system in the amygdala is implicated in compulsive substance use during later stages of SUD, when a negative emotional state is the motivational factor to continue drug use [12] (negative reinforcement).

## 2.2. Psilocybin

In the 1950s, a group of drugs was discovered that had the potential to alter consciousness. These new mind altering drugs were called hallucinogens. The most extensively studied hallucinogen is LSD. Several studies suggested an anti-SUD potential, by showing improvements in self-acceptance and interpersonal relationships, and reductions in craving and alcohol use in the treatment of alcohol dependence [21,22]. However, the lack of randomized, double-blind, placebo-controlled designs hamper researchers to draw firm conclusions concerning LSD's efficacy in alcohol dependence [23,24]. Moreover, several studies did not find evidence for the efficacy of LSD in the treatment of alcohol dependence [25–27]. As a result of its recreational popularity during the 1960s, its abuse potential LSD was banned in 1967, greatly reducing scientific research in this field. Recently, another hallucinogen, psilocybin, has gained popularity in neuropsychological research. Psilocybin, a hallucinogenic substance in psilocybin-containing mushrooms, has been shown to increase trait openness [28], cognitive and behavioral flexibility [29], and ratings of positive attitude, mood, social effects, and behavior at the 2-month and 14-month follow-up [30]. One double-blind study even reported persistent positive changes in attitude and behavior after a single dose of psilocybin for up to 25 years [31]. Psilocybin has also been shown to decrease depressive symptoms in terminally ill cancer patients [32]. These findings suggest that psilocybin might be a valuable compound for the treatment of psychiatric conditions.

Similar promising findings have been observed in addiction research (see Table 1), where participants typically receive 0.3–0.4 mg/kg of psilocybin in two to three sessions. A recent pilot study in alcohol-dependent patients on the efficacy of psilocybin in alcohol dependence showed a

significant reduction in both percentage of drinking days and heavy drinking days, with large effect sizes [33]. Furthermore, a recent study investigating psilocybin in tobacco dependence demonstrated that 80% of the participants had quit smoking after a 6-month follow-up, thereby substantially exceeding success rates for other behavioral and/or pharmacological therapies [34]. In the latter study, participants were also asked why they thought psilocybin helped in quitting smoking. The most common reasons were 'changing orientation toward the future, so that long-term benefits outweighed immediate desires (73%); strengthening participants' beliefs in their ability to quit (73%); and changing life priorities/values, such that smoking was no longer more important than quitting (68%)'.

It is important to note that both studies on the effect of psilocybin in SUD patients did not assess the effect of psilocybin on relapse rates after a period of abstinence. This is a lack of knowledge in the current literature that future studies should address. However, several additional studies do provide some supportive evidence for the therapeutic potential of psilocybin for SUD treatment and relapse prevention [35,36]. In a study by Hendricks et al. [36], it was found that hallucinogen use predicted reduced recidivism among substance-involved offenders and it was suggested that hallucinogens may promote alcohol and other drug abstinence and prosocial behavior. In order to examine the mechanistic contributions of hallucinogens, Burdick and Adinoff [35] have proposed an experimental design for a clinical trial to evaluate the efficacy of psilocybin in addiction treatment.

As outlined above, an elaborate (mechanistic) theory explaining the potential mechanism of psilocybin's efficacy, as a treatment for SUD, is currently lacking. This review aims to discuss scientific evidence for the potential therapeutic effects of psilocybin for SUD. Current findings suggest that psilocybin may support drug-dependent individuals in overcoming their SUD [37]. Potential mechanisms are discussed.

### 2.2.1. History of psilocybin-containing mushroom use

Psilocybin is the main psychedelic ingredient of mushrooms of the genus *Psilocybe* [38] that has been used both in the lay scene, as in various studies for the treatment of anxiety and obsessive compulsive disorder [32,39]. Ritual use of psilocybin-containing mushrooms across the globe dates back millennia and is still regionally practiced today. Robert G. Watson first introduced these mushrooms to the Western society in 1957. Shortly after being introduced to the general public, it was scheduled as a class I drug in 1970 and human experiments steadily terminated. However, given its limited side effects (see

**Table 1.** Evidence table summarizing the results of human studies on the use of psilocybin for treating substance use disorders. Participants in both studies received similar doses of psilocybin, however, at different timepoints after the start of PST.

Author	Type of SUD	Sample size	Follow-up period	Results	Administration procedure
(Bogenschutz et al. [33])	Alcohol dependence	$n = 10$	Weeks 4, 8, 12, 24, and 36	Significant reduction in percentage drinking days and heavy drinking days	Session 1: 4 weeks after PST 0.3 mg/kg Session 2: 8 weeks after PST 0.4 mg/kg
(Johnson et al. [34])	Tobacco dependence	$n = 15$	Weeks 2–15, 6-month follow-up	80% abstinence at 6-month follow-up	Session 1: 5 weeks after PST 0.29 mg/kg Session 2: 7 weeks after PST 0.43 mg/kg Session 3: 13 weeks after PST 0.43 mg/kg

PST: Psychosocial treatments; SUD: substance use disorders.

below) and pharmacological properties, human experimental research on the neuropsychological effects of psilocybin has revived since the late 1990s (for review [40,41]).

### 2.2.2. Metabolism and minimal toxicity of psilocybin

The prodrug psilocybin is rapidly dephosphorylated by alkaline phosphatase [42] in the intestinal mucosa to psilocin. The dephosphorylation of psilocybin is not essential for the psychotropic action but does increase its potency by a factor 1.4 [42]. After absorption, psilocybin is distributed in all tissues, including the brain, where it exerts its psychedelic properties. It is then glucuronidated by endoplasmic enzymes and subsequently excreted from the body by the kidneys (65%), liver, and intestine (15–20%) [43]. Although some authorities warn about the dangers of using psilocybin-containing mushrooms, multiple studies and clinical trials revealed a low toxicity of psilocybin [44,45]. For example, studies in rats and pigs showed no evidence of toxicity for heart and intestine cells [46], nor for the brain [47]. We encountered two reported fatalities of psilocybin use. In one case, a person died after ingestion of an extremely high dose of *Psilocybe semilanceata*, resulting psilocybin plasma levels of 4 µg/mL [48]. In another case, a heart transplant recipient appeared to have plasma psilocin levels of 30 µg/mL [49]. Despite the mild physiological effects, including hypertension and tachycardia, it cannot be excluded that extremely high doses of psilocybin cause LSD-overdose-like effects such as hyperthermia, respiratory failure, or even coma [50]. It is however unclear at what plasma levels, such effects occur.

### 2.2.3. 5-HT neuropharmacology of psilocybin

The structural formula of psilocybin is very similar to 5-HT (Figure 1). Therefore, it is not surprising that psilocybin binds with high affinity to 5-HT receptors. The neurophysiological action of psilocybin has been found to be dependent on 5-HT receptor distribution in different cell types. This can consequently lead to increased or decreased neuronal activity depending on the specific brain area [51].

Psilocybin binds to multiple 5-HT receptors, but it has the highest affinity for 5-HT<sub>2A</sub> ( $K_i = 6$  nM) and to a lesser extent at 5-HT<sub>1A</sub> receptors ( $K_i = 190$  nM) [53]. A study by Vollenweider et al. [54] reported that pretreatment with ketanserin, a selective 5-HT<sub>2A</sub> receptor antagonist, dose dependently blocked the psychological effects of psilocybin. Similarly, risperidone, a 5-HT<sub>2A/D2</sub> receptor antagonist, completely blocked the psychotropic effects of psilocybin [54]. Animal studies in rats showed that various 5-HT<sub>2</sub> antagonists block the stimulant

effects of LSD [55]. Fiorella et al. [55] also found a correlation between 5-HT<sub>2A</sub> antagonist binding affinity and the degree of stimulant effect of the hallucinogen. Another study reported similar findings regarding the behavioral effects of hallucinogens; a near perfect correlation was found between the behavioral potency of hallucinogens and its affinity to the 5-HT<sub>2A</sub> receptor [56].

Whereas the 5-HT<sub>2A</sub> receptor plays a key role in the characteristic effects of many hallucinogens, it has been suggested that in animals, the nonselective interaction of hallucinogens with other 5-HT receptors contributes to behavioral effects such as lateral head weaving, hind limb abduction, backward locomotion, and lower lip retraction (for review, see Halberstadt and Geyer [57]). A study by Strassman [58] suggested that 5-HT<sub>1A</sub> receptor agonism may act to buffer 5-HT<sub>2A</sub>-mediated psychedelic effects.

### 2.2.4. Neuroanatomical localization of 5-HT receptors

The neuroanatomical distribution of 5-HT receptors explains the behavioral effect of psilocybin. Several studies show high 5-HT<sub>2A</sub> receptor densities in cerebral cortical areas including the frontal, parietal, temporal, and occipital lobe, which are largely involved in memory, attention, perceptual awareness, thought, language, and consciousness as well as cognitive control [59]. Key behavioral components of 5-HT function in cognitive control include being able (1) to hold information in mind including complicated representational structures, to mentally manipulate that information, and to act on the basis of it, (2) to act on the basis of choice rather than impulse, exerting self-control by resisting inappropriate behaviors, and (3) to quickly and flexibly adapt behavior in response to changing environments [60].

The amygdala, a brain area that functions as a sensory interface during emotional learning, also shows high expression of 5-HT<sub>2</sub> receptors. Specifically, the 5-HT<sub>2A</sub> receptor is expressed on both pyramidal (i.e. excitatory) and non-pyramidal neurons in the amygdala [61] and plays a critical role in the formation of emotional memories [62]. The amygdala, together with the ventral striatum, is believed to play an important role in associative processes in SUD through interactions between primary reinforcement, psychomotor activation, Pavlovian conditioning, and cue-induced drug seeking behavior [63].

The 5-HT<sub>2A</sub> receptors are also expressed in the PVN and implicated in the regulation of the HPA-axis and anxiogenic responses [64]. Chronic stress desensitizes these receptors [65], whereas withdrawal from drug self-administration has been associated with 5-HT<sub>2A</sub> receptor supersensitivity in the

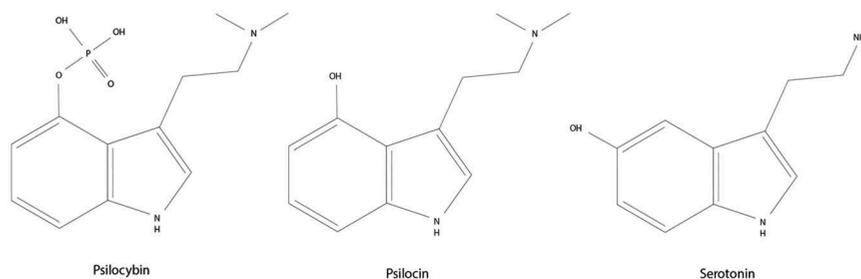


Figure 1. Chemical structures of psilocybin, psilocin, and its endogenous analogue serotonin. Edited from Stebelska [52].

PVN [66]. 5-HT<sub>2A</sub> receptors may thus strongly influence the emotional state of an individual and involve emotional disturbances observed in SUD.

Finally, 5-HT<sub>1A</sub> receptors are largely found in the hippocampus, septum, neocortex, raphe nucleus, and amygdaloid nuclei [67], which are involved in mediating cognitive and emotional processes, respectively. High densities of 5-HT<sub>1A</sub> binding have also been found in the limbic systems of several mammalian species including humans. As a result, also 5-HT<sub>1A</sub> receptors are involved in mediating the emotional state of individuals and patients with SUD.

### 2.3. Putative modes of action of psilocybin in SUD

The predominant action of psilocybin on central 5-HT<sub>2A</sub> and 5-HT<sub>1A</sub> receptors suggests that emotional and cognitive processes regulated by brain regions containing high levels of these serotonergic receptors may play an important role in the mode of action of the drug. Indeed, several authors suggest a dual process model for SUDs, where an imbalance in cognitive control functions and emotional processes contributes to the development and persistence of SUDs. This model aligns well with the National Institute of Mental Health (NIMH) roadmap for bridging the gap between neurobiological insights in the mechanisms and the clinical classification of mental disorders, using Research Domain Criteria (RDoC; see also Insel, Thomas R.; Lieberman, Jeffrey A. (13 May 2013). 'DSM-5 and RDoC: Shared Interests' (Press release). NIMH). Below, we will elaborate on how psilocybin may exert its anti-addictive properties, within this conceptual framework of SUDs. We especially emphasize on psilocybin's potential effects on negative emotional states and stress (RDoC domain: negative valence systems), and cognitive inflexibility and compulsivity (RDoC domain: cognitive systems), and two key features displayed in patients with SUD.

#### 2.3.1. Psilocybin: effects on negative emotional states and stress

Substance dependence is strongly associated with negative affect and stress, as also observed in major depressive disorder (MDD) [7]. Similar to MDD, it has been shown that individuals suffering from SUD suffer from persistent dysregulations in their emotional (amygdala-mediated) and stress (HPA-axis-mediated) systems [68]. As outlined above, the amygdala, which is strongly innervated by serotonergic neurons [69], is known to be involved in the processing of emotions and related memories. The 5-HT<sub>1A</sub> and the 5-HT<sub>2A</sub> receptors play a central role in these processes [70,71]. Increased prefrontal cortex 5-HT<sub>2A</sub> and decreased hippocampal 5-HT<sub>1A</sub> receptor expression and/or binding have been shown to contribute to the pathophysiology of negative affect, depression, and suicide [72,73]. This has led several researchers to propose that postsynaptic 5-HT<sub>1A</sub> and 5-HT<sub>2A</sub> receptors exert opposing effects in the regulation of mood [74]. A disturbed balance between these receptors has been thought to contribute to depression [75] but may also be relevant for SUD. Since restoring this balance is thought to be necessary for antidepressant action [41], this may also be true for the treatment of SUD.

A recently published fMRI study found decreased amygdala reactivity during acute psilocybin treatment which was associated with an increase in positive mood in healthy volunteers [76]. Similarly, a study on the physiological and psychological effects of low-dose psilocybin administration in terminal cancer patients showed a sustained reduction in trait anxiety that reached significance at the 1- and 3-month points after treatment [32]. These phenomena may also be relevant for the normalization of amygdala hyperactivity in SUD associated with cue-induced drug craving and anxiety [77]. Although SUD and cancer are two entirely different diseases, psilocybin may thus exert long-term anxiolytic effects in humans, including SUD patients.

Chronic stressful circumstances are represented by a dysregulation and increase in basal cortisol levels. A study by Ouellet-Morin et al. [78] showed that maltreated/bullied children had significantly lower cortisol responses to a stressor compared to children who were not bullied or maltreated. Furthermore, among maltreated/bullied children, lower cortisol responses were, in turn, associated with more behavioral and social problems [78]. Early life adversity and aberrant function of the HPA-axis have also been associated with MDD [79] and SUD [80], although the precise mechanisms are not fully clear yet. 5-HT receptor activation in the hypothalamus has been suggested to induce CRF secretion and concomitant HPA-axis activation. For example, the 5-HT<sub>2A</sub> receptor agonist DOB ((+)-1-(2,5-dimethoxy-4-bromophenyl)-2-aminopropane) was able to activate the HPA-axis and dose dependently increase plasma ACTH and cortisol [81]. Multiple studies showed that psilocybin could also temporarily increase cortisol, ACTH, prolactin, and thyrotropin levels without a stress test, which returned to normal after 5 h [82]. Although an increase in cortisol levels seems contradictory to achieving stress reduction, studies by Lupien et al. [83] showed cortisol is necessary for learning and memory in humans. A psilocybin-induced cortisol spike may activate large-scale brain networks, which are clusters of interconnected brain regions mediating a well-defined cognitive function. Networks playing a key role in SUD [84] involve the default mode network (DMN, including the medial prefrontal cortex, posterior cingulate cortex, precuneus, hippocampus, and inferior parietal cortex), the executive control network (ECN, including the dorsolateral prefrontal cortex, frontal eye fields, and dorsal posterior parietal cortex), [85] and the salience network (SN, including the amygdala, insula, anterior cingulate cortex, and ventral striatum) [86]. This triple network model proposed by Menon [86] and involving the SN, DMN, and ECN was adapted by Sutherland et al. [87] who suggested that the SN is important for dynamic switching between the DMN and ECN. When there is a cortisol spike, the SN is immediately activated, in order to steer attention toward the stressor. A study published recently by Kraehenmann et al. [88] found that psilocybin reduced stressor-induced modulation of amygdala connectivity (part of the SN) which may explain the potential of psilocybin to shift emotional biases away from negative during emotional processing [89]. This may also affect the reallocation of the available attentive resources to other networks, like the DMN and ECN. Data suggest that the DMN is activated within 100 min after

psilocybin administration [82]. Activation of the DMN leads to an introverted phase (directing thoughts and feelings toward oneself). During this period, the initial stress and subsequent withdrawal induced anxiety-related and depression-like symptoms may be emotionally processed. Finally, the ECN is activated, which occurs 60–90 min after onset of a stressor. The ECN allows one to orient to external tasks and improve focused attention and working memory [90].

### 2.3.2. Role of 5-HT<sub>2A</sub> and 5-HT<sub>1A</sub> in cognitive inflexibility and compulsivity

Cognitive flexibility enables an individual to switch behavior in response to environmental changes. Such a disengagement from ongoing behavior requires multiple cognitive components of decision-making. It is clear that the ability to change a certain behavior is imperative in order to resolve SUD. Multiple studies found that both psilocybin and LSD enhanced reversal learning in both rats and primates [91,92]. Of interest, behavioral inflexibility is strongly modulated by 5-HT<sub>2A</sub> receptors. It has been demonstrated that 5-HT<sub>2A</sub> receptor antagonism impairs behavioral flexibility by increasing perseveration [93], suggesting that 5-HT<sub>2A</sub> agonism has a beneficial effect on behavioral flexibility. Indeed, 5-HT<sub>2A</sub> receptors in the orbitofrontal cortex facilitate reversal learning [94]. The 5-HT<sub>1A</sub> receptor is also implicated in behavioral flexibility but may be limited to restore flexibility when impaired in disease models [95]. Behavioral flexibility is furthermore dependent on the prefrontal cortex, insula, basal ganglia, anterior cortex [96], and posterior parietal cortex [97]. Since these brain regions are components of the SN and ECN, respectively, it is possible that psilocybin increases behavioral flexibility by reducing SN and increasing ECN activity (see Section 2.3.1).

### 2.3.3. Side-effects and addictive properties of psilocybin

The side effects of using psilocybin mainly depend on personal expectations and the environmental setting in which a subject uses it [98]. A pooled analysis study investigating the effects of different predictor variables on the acute response to psilocybin in healthy volunteers found that being in an emotionally excitable and active state immediately before drug intake, and having experienced few psychological problems in the weeks before were most strongly associated with pleasant and mystical-type experiences [99]. Altered perceptions, including hallucinations, and intensified emotions can result in dangerous behavior during nonmedical administration [47]. Such complications can usually be prevented by the following rules: proper education before administration, administration in a calm and safe environment, and guidance of an experienced user during the experience [47].

It has been shown that the use of hallucinogenic substances may accentuate or trigger psychotic symptoms or evoke non-specific psychotic episodes in patients suffering from depression, schizophrenia, or psychosis [100]. However, it is not likely that hallucinogenic substances cause psychiatric conditions in non-predisposed individuals. The prevalence of prolonged psychiatric symptoms after use of LSD has been investigated in healthy subjects and psychiatric patients. It was estimated that 0.08–0.09% of the healthy volunteers and 0.18% of psychiatric patients experienced prolonged psychiatric symptoms as a consequence

of LSD use [100]. Prolonged psychosis in healthy subjects after a single dose of psilocybin is extremely rare and in most cases associated with a psychotic predisposition [47]. A thorough medical and psychiatric screening and strong interpersonal support from session monitors before, during, and following sessions are key factors in minimizing long-lasting adverse psychological effects of psilocybin administration.

The risk of substance dependence or addiction to psilocybin appears to be very low [101]. Users of psilocybin quickly build up a tolerance to the reinforcing effects of the substance. However, in humans, psilocybin was reported not to cause craving or withdrawal [47]. In a recent animal study on self-administration in monkeys, three out of four animals showed very low self-administration rates above placebo [102]. For these animals, psilocybin initially had a reinforcing effect. Animals were unable to maintain self-administration behavior. These observations may be explained by the fact that psilocybin does not directly affect the mesolimbic dopaminergic pathway and thus does not activate the above a brain-reward system directly.

## 3. Summary and conclusion

Taken together, we propose here that psilocybin may have therapeutic effects in the treatment of SUD. With the reported limited amount of side effects, and potential beneficial effects of psilocybin in SUD, we strongly believe that there are valid reasons to further investigate the therapeutic efficacy and safety of psilocybin as a potential SUD treatment. We specifically hypothesize two mechanisms of action of psilocybin that might mediate its anti-addictive properties. On the one hand, psilocybin may exert its anti-addictive properties by beneficial effects on negative emotional states and stress. On the other hand, psilocybin may improve cognitive inflexibility and compulsivity. These effects may be mediated through binding of psilocybin to central 5-HT<sub>2A</sub> and 5-HT<sub>1A</sub> receptors.

Given that psilocybin affects 5-HT<sub>2A</sub> receptor-mediated signaling implicated in emotional processes, the neuroendocrine system, and behavioral flexibility, we hypothesize that psilocybin overall may improve cognitive functioning and alleviate anxiety-related and depression-like symptoms associated with SUD. Research on the efficacy of psilocybin on SUD is still limited to a handful of published studies to date. As a result, many important questions related to the use of psilocybin as a complement to current treatment of SUD, and its working mechanisms remain unanswered. For instance, it is unknown if and how psilocybin interacts with existing behavioral and pharmacological treatments for SUD. Qualitative analysis of experiences of people that used psilocybin may also shed some light on the individual processes in overcoming their SUD. Clearly, before psilocybin can be implemented as a treatment option for SUD, more extensive research is needed to address these and other issues. We have outlined further outstanding issues in our expert opinion.

## 4. Expert commentary

Most research on psychedelics was performed in the 1950–1970s, but these substances became illegal because of their hallucinogenic effects. Many studies tested the potential

of the mind-altering effects of psychedelics for treating psychiatric disorders, including SUD. Several studies have reported significant reductions in substance use and craving in SUD patients, after administration of psychedelics, including psilocybin. However, many of these studies lacked a double-blind controlled design, which limits the level of evidence. Furthermore, several studies did not confirm efficacy of psychedelics in SUD. Nonetheless, given the recently published positive findings and neuropharmacological properties of psilocybin outlined above, we believe that psilocybin holds potential for the treatment of SUD.

Recently, several studies reported positive results of psilocybin in amongst others alcohol and nicotine dependence. Considering the previous conflicting results on the efficacy of psychedelics in SUD, these recent positive findings with psilocybin need confirmation in well-designed placebo-controlled randomized trials employing a large sample size. It is also important to determine whether the efficacy of psilocybin is dependent on the type of SUD. It is conceivable that psilocybin, acting through 5-HT receptors, differentially influences psychostimulant (5-HT-dependent) and opiate (5-HT-independent) SUD. It also remains to be clarified whether and how 5-HT<sub>2A</sub> receptors modulate SN, DMN, and ECN activity in SUD, and whether genetic variation within the 5-HT<sub>2A</sub> and 5-HT<sub>1A</sub> receptors causes individual differences in responsivity to psilocybin. Also, preexisting trait characteristics, including anxiety and personality, may be of influence on the efficacy of psilocybin, as these traits may be shaped by neural network patterns that are targeted by psilocybin. Furthermore, it is not clear yet whether gender plays a role in the efficacy of psilocybin for SUD. Gonadal hormones interact with cortisol and thereby may influence the psilocybin-induced cortisol spike and the subsequent cascade of neural network activation patterns. Along the same line, it remains to be determined whether changes in HPA-axis function in different types of SUD patients influence the efficacy of psilocybin. Studies are required to unravel the anti-addictive potential of psilocybin. In animal studies, this can be addressed by studying whether psilocybin reduces the self-administration of substances of abuse and specifically the drug-, cue-, and stress-induced reinstatement of drug-seeking behavior. A controversial question is whether psilocybin use may have preventive effects for the development of SUDs, for example when used by adolescents and young adults. Animal studies are well suitable to explore preventive efficacy of psilocybin for SUDs and investigate toxicity for the developing brain in adolescents and young adults. In humans, the efficacy of psilocybin to reduce relapse during 6–12 month longer follow-up measures need to be assessed. Ultimately, such studies and research into the working mechanisms of psilocybin may identify new treatment targets for the discovery of new medications.

## 5. Five-year view

We expect that the field of psychedelic research will significantly increase over the coming years. The recreational use of psychedelics in America has remained popular among younger adults since the 1960s with prevalence rates as high as 20%. This shows that the subject of psychedelics is still very alive in the Western society. What is more, last year marijuana

has been legalized in several US states. Hence, there is a shift in how society perceives these mind-altering substances. It is possible that psychedelic drugs are being used as a form of self-medication by some individuals. It is interesting for future research to study what kind of psycho-behavioral background regular users have and why and with whom they use it. This may shed more light on the motivation and perhaps some psycho-emotional modes of action of psilocybin.

## Key issues

- Psilocybin is a hallucinogen with low risk of toxicity and dependence
- Psilocybin's chemical structure is similar to that of serotonin
- Psilocybin acts predominantly through the 5-HT<sub>2A</sub> receptor, and to a lesser extend through the 5-HT<sub>1A</sub> receptor
- Psilocybin potentially exerts effects on the negative valence system and on cognitive systems

The serotonergic action of psilocybin may contribute to the reduction in addictive behaviors by enhancing cognitive control and increasing control over emotions.

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## Declaration of interest

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## Contributors

BdV drafted the manuscript, JH guided the writing proces, MV and AS critically read and edited the manuscript.

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