Commentary

Microdosing psychedelics: More questions than answers? An overview and suggestions for future research

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Abstract

Background: In the past few years, the issue of 'microdosing' psychedelics has been openly discussed in the public arena where claims have been made about their positive effect on mood state and cognitive processes such as concentration. However, there are very few scientific studies that have specifically addressed this issue, and there is no agreed scientific consensus on what microdosing is.
Aim: This critique paper is designed to address questions that need to be answered by future scientific studies and to offer guidelines for these studies.
Approach: Owing to its proximity for a possible approval in clinical use and short-lasting pharmacokinetics, our focus is predominantly on psilocybin. Psilocybin is allegedly, next to lysergic acid diethylamide (LSD), one of the two most frequently used psychedelics to microdose. Where relevant and available, data for other psychedelic drugs are also mentioned.
Conclusion: It is concluded that while most anecdotal reports focus on the positive experiences with microdosing, future research should also focus on potential risks of (multiple) administrations of a psychedelic in low doses. To that end, (pre)clinical studies including biological (e.g. heart rate, receptor turnover and occupancy) as well as cognitive (e.g. memory, attention) parameters have to be conducted and will shed light on the potential negative consequences microdosing could have.

Keywords
Psychedelics, microdosing, psychoactive substances

Background

Psychedelics are a class of psychoactive substances that induce complex behavioural, psychological and physiological effects primarily through activation of serotonin 5-HT_{2A} receptors. In the past few years, the issue of 'microdosing' psychedelics has been openly discussed in the public arena with several books (Cruz, 2017; Kumar, 2016; Waldman, 2017) claiming value to the authors who tried this concept. However, there are very few scientific studies that have specifically addressed this issue, and there is no agreed scientific consensus on what microdosing entails (Cameron et al., 2019; Horsley et al., 2018). This paper is designed to address questions that need to be answered by future scientific studies and to offer guidelines for these studies. Although a number of classic psychedelics exist, two of them, lysergic acid diethylamide (LSD) and psilocybin, are allegedly most frequently used to microdose. The following review focuses predominantly on psilocybin due to its proximity for a possible approval in clinical use and short-lasting pharmacokinetics (Passie et al., 2002) in comparison with LSD (Dolder et al., 2017). However, where relevant and available, data for other psychedelic drugs are also mentioned.

As early as the 16th century, low doses of psilocybin, '*teonanacatl'* or sacred mushroom, were used medically (Schultes, 1940). Bernardino de Sahagún, a Franciscan friar during the period of the Spanish conquest of the Americas (1519–1521), reported that, 'teonanacatl were … medicinal for fevers and for rheumatism. Only two or three need to be eaten. Those who eat them see visions and feel a faintness of the heart. And they provoke lust to those who eat a number, or even a few, of them'. However, by 1640, 94% of the Aztec population was wiped out and alongside them, the traditions involving 'teonanacatl'. Of note, the mentioning of visions here suggests this ancient 'low-dose' use does not refer to what is currently seen as microdosing, something that will be addressed below.

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Psychedelic studies underwent a significant expansion following the discovery of the mind-altering properties of LSD by Albert Hofmann in 1943 (Hofmann, 1970). The subsequent growth of psychedelic use allegedly had a profound effect on innovation in science and technology. A popular example is that of Francis Crick, one of the co-discoverers of the double-helix structure of DNA, who used LSD, though this use was never confirmed nor denied by him (Roberts, 2008). Furthermore, Kary Mullis, who discovered a means to automate the polymerase chain reaction, claimed that the idea came to him after using LSD (Doyle, 2002). These discoveries greatly advanced the field of genetic research (Luke, 2006). In this atmosphere of innovation, Frederick Terman was appointed as Provost of Stanford, 1955–1965. During his tenure, Terman 'set out to create a community of technical scholars in Silicon Valley' (Leslie and Kargon, 1996). This community developed alongside the psychedelic capital of the world, San Francisco, and over time technology and psychedelics began to merge. By 2005, the founder of Apple and one of the most influential figures in Silicon Valley, Steve Jobs, highlighted that LSD had played a pivotal and transformative role in his life (Dormehl, 2012).

Although there was accumulating evidence to suggest that the intake of psychedelics led not only to hallucinations but also to an improvement of cognition and creativity, scientific progress in the field was prohibited by government agencies on account of the growing political concern over the recreational use of psychedelics (Belouin and Henningfield, 2018). Thus, the only study investigating psychedelics in problem solving was ended by the US Food and Drug administration (FDA) in 1966 (Harman et al., 1966). However, James Fadiman, a young researcher in this study, continued his research after the UN Convention on Psychotropic Substances of 1971 banned psychoactive substances and bundled his knowledge into a book, which now acts as a guide for those interested in microdosing. His book *The Psychedelic Explorer's Guide: Safe, Therapeutic, and Sacred Journeys* (Fadiman, 2011) published in 2011, is often referred to as a protocol for those practising microdosing. Of note, no study to date has revealed statistically significant effects of microdosing on creativity under placebo-controlled circumstances (Passie, 2019).

Although microdosing became prominent due to the belief it improved cognition, a growing number of individuals began to microdose psychedelics to improve conditions of pain (Johnstad, 2018), cluster headache or migraine (Andersson et al., 2017). It seems that the efficacy of microdosing may derive from its non-psychedelic dose range, which provides treatment without affecting cognition. Individuals also reported relief of pain with a long-term psychedelic microdosing regimen (Johnstad, 2018). Thus, psychedelic microdosing might constitute a different paradigm to single psychedelic therapeutic sessions with *macrodoses* where the nature and content of the experience plays a key role in predicting therapeutic outcome (Roseman et al., 2018; Schenberg, 2018). However, many questions remain about the definition, safety, potential mechanism and future research involving microdosing.

Question 1: What does microdosing mean?

The term microdosing is not a uniquely psychedelic term. In pharmacology, microdosing is a process used in drug development (Lappin and Garner, 2008) and drug selection (Lappin et al., 2006) where a minute dose of a substance is used to assess the pharmacokinetics of a drug. A microdose, in this regulatory arena, has been defined by a position paper from the European Medicines Agency 2004 (EMEA, 2003), guidelines from the U.S. Food and Drug Administration in 2006 (FDA, 2006) and the Ministery of Health, Labour and Welfare in Japan in 2008 (MHLW, 2008), and the current definitive international guideline in 2009 (ICH, 2009) as being a dose of drug that is 1% of the pharmacologically active dose, up to a maximum of 100 μg. Thus, psychedelic microdosing ('5–10 μg of LSD' (Fadiman, 2011)) would be 5–10% of a usual psychoactive dose and lie between a full pharmacological dose (100%) and a 'pharmacological microdose'.

Microdosing psychedelics has been described in a similar manner by different individuals. Fadiman describes it as a practice 'to use sub-threshold doses of psychedelic drugs in an attempt to enhance cognitive tasks, to boost physical energy levels, to promote emotional balance, and to treat anxiety, depression and addiction' resulting in typically subtle though noticeable effects (Fadiman, 2011). Similarly, Aylet Waldman in her book (Waldman, 2017) states the same intention for microdosing but describes the process as 'the act of integrating sub-perceptual doses of psychedelic drugs, in your weekly routine'. In addition, Johnstad emphasizes that 'to microdose with a psychedelic drug means to take a dose small enough to provide no intoxication or significant alteration of consciousness' (Johnstad, 2018).

Thus, the term 'microdosing' appears to consist of three components:

1. The use of a low dose below the perceptual threshold that does *not impair* 'normal' functioning of an individual.
2. A procedure that includes multiple dosing sessions.
3. The intention to improve well-being and enhance cognitive and/or emotional processes.

Existing dosing categories for psychedelics when used in research are *very low dose, low dose, medium dose*, and *high dose* (Table 1). A microdose has been defined as approximately one-tenth to one-twentieth of a recreational dose, varying within and between substances, so it can be seen as being somewhat below a very low dose. Although microdosing of psychedelics does not have an agreed scientific definition, we have decided to continue to use the term because of its prevalent societal use. Hopefully, this paper will help to facilitate research towards establishing it as a scientific construct.

The most widely distributed species of psychedelic mushrooms are *Psilocybe cubensis* and those of the genus *Copelandia*, which consists of 12 species (Guzmán et al., 1998). The psilocin (the active metabolite of psilocybin) and psilocybin content in the whole body of these mushrooms when dried was estimated to be in the range of 0.14–0.42% (psilocin) and 0.37–1.30% (psilocybin) for *P. cubensis* and 0.43–0.76% (psilocin) and 0.08–0.22% (psilocybin) for *Copelandia*, respectively. Thus, the former is more psilocybin-rich than the latter, and the latter contains more psilocin compared to the former (Tsujikawa et al., 2003). The *Psilocybe semilanceata* is the most common British species. This mushroom only contains psilocybin, in the range from 0.17 to 1.96%, as shown by one Norwegian analysis (Christiansen et al., 1981; Rumack and Spoerke, 1994). These data show that the psilocybin concentration varies between and within species but is also dependent on the time of collection, the preservation of the material and growth conditions. User reported recreational doses depend on the species and experience of the user (Rumack and Spoerke, 1994).

Table 1. Varying doses of psychedelic compounds used in preclinical and clinical studies.

Substance	Subjects/participants (animal/human)	Route of administration	Microdose	Very low dose	Low dose	Medium dose	High dose
Psilocin (Hasler et al., 2004; Wackermann et al., 2008)	Human (both studies)	Oral	<1 mg	3.15 mg	8 mg	15 mg	22 mg
LSD (Dandiya et al., 1969)	Rats	Intraperitoneally	10–25 μg	30– 40 μg	60–110 μg	150 μg	200+ μg
Ibogaine HCl (Glick et al., 2000; Lotsof and Wachtel, 2002; Schechter and Gordon, 1993)[a]	Rats Humans[a]	Intraperitoneally Oral[a]	200 mg	300–400 mg	700 mg	1400 mg[a]	2800 mg
DMT (Shulgin, 1976)	Humans	Intramuscular injection	6 mg	10 mg	20 mg	30 mg	50–70 mg[b]

Per kilogram dose values have been converted to values for a 70-kg person. These doses are approximate values.
[a]Study conducted in humans using a single oral dose of 1400 mg.
[b]When inhaled, 30 mg would be considered a high dose.

A hallucinogenic dose of dried *P. cubensis*, for example, is between 3 and 5 g (Rumack and Spoerke, 1994). These values equate to a recreational dosing range of 8.6 to 14.7 mg of psilocin per dose. Thus, a microdose would range from 0.43 to 0.73 mg of psilocin per dose because a microdose of psilocybin is generally one-tenth of a full dose (Fadiman, 2011). That positions a recreational dose of psilocin between a low and medium dose and a microdose below a very low dose. However, variations in psilocin content between doses of dried mushroom may be seen due to variations between individual fungi within a species. A microdose of LSD ranges between 10 and 20 μg with 20 μg being the upper limit that might already produce perceptual changes in some. A microdose of ibogaine hydrochloride is approximately 25 mg (Kroupa and Wells, 2005), and when smoked, that of *N,N*-dimethyltryptamine (DMT) is approximately 6 mg (May, 2018).

Question 2: What microdosing schedules have been used?

The data presented here were collected using a search of microdosing protocols that included books, online fora and surveys. The keywords of this search included microdosing, microdosing protocols, microdosing approaches and psilocybin microdose. In this search, it was found that users mainly followed three approaches. The most popular of these was the Fadiman approach, outlined in his book (Fadiman, 2011), which involves two consecutive dosing days followed by two non-dosing days. Another popular approach involves 'weekday' dosing, i.e. from Monday to Friday and not dosing on Saturday and Sunday. Additionally, some users indicated that they followed a balanced low/microdose approach, which involved dosing every other day. Dosing periods ranged from 1 week to 2 years. This variation in microdosing schedules was confirmed by a recent survey which demonstrated that half of the respondents who microdosed came up with their own schedule (Hutten et al., 2019).

Question 3: What controlled studies have been done so far?

The first placebo-controlled LSD microdosing study was published recently (Yanakieva et al., 2018). Findings showed a delay of time perception in the absence of self-rated effects on perception, mentation and concentration after administration of single doses of 5, 10, and 20 μg LSD. To our knowledge there has been only one published study designed specifically to measure the effects of psilocybin microdosing per se (Prochazkova et al., 2018) where the effects of psychedelic mushrooms were explored in a recreational setting. This study suffers from a number of methodological issues, particularly the lack of a placebo control as well as uncertainty over dose taken. However, there have been several more controlled studies where a low dose of psilocybin has been used as a control for a regular dose; these are presented below.

For example, Hasler and colleagues (2004) compared four doses of psilocybin in healthy humans in a placebo-controlled experimental design and found slight physiological and psychological differences between single administration of placebo and a very low dose (VLD) (Hasler et al., 2004). A VLD was defined as 45 μg/kg p.o., equating to approximately 2.3 mg of psilocin for an average 70-kg human. VLD was compared with a low dose (LD), a medium dose (MD) and a high dose (HD) defined as 115, 215 and 315 μg/kg p.o., respectively. Although most physiological measures were similar between the VLD dose and placebo, a significant decrease was seen in maximum heart rate at the 6-hour point after VLD administration. Acute self-rated/self-reported psychological responses of VLD included slight drowsiness, increased sensitivity and intensification of pre-existing mood states; an increase in introversion compared to placebo was only shown for the MD and HD at peak drug effect, 95 minutes post-administration.

Building on that, Griffiths and colleagues (2011) investigated the effects of psilocybin in varying doses where each participant received five dosing sessions, spread across 1-month intervals (Griffiths et al., 2011). The doses used were 0, 5, 10, 20 and 30 mg/70 kg. Using a Monitor Rating Questionnaire with a 5-point scale, they found that a dose of 5 mg/70 kg increased stimulation, distance from ordinary reality and sense of peace. Intensity, somaesthesia, affect, perception, cognition and volition measured on the Hallucinogen Rating Scale all increased after administration of a 5 mg/70 kg dose. In other words, they did not find a dose without psychological effects. Interestingly, when using an 11 mg/70 kg and 15 mg/70 kg dose of psilocybin, Lewis and colleagues (2017) found a significant decrease in global cerebral blood flow in the frontal, parietal, temporal, limbic, cingulate and occipital cortex, insula, caudate, putamen, pallidum, amygdala, hippocampus and thalamus (Lewis et al., 2017). This may relate to the psychological effects seen with lower doses.

Psychological effects of microdosing have been regularly reported by users after multiple administrations of psilocybin. Independent accounts from online fora and surveys (Fadiman and Korb, 2019; www.thethirdwave.co; www.dmt-nexus.me, 2018; www.reddit.com, 2018) reveal that users report improvements in energy, mood, cognition, concentration, management of stress, creativity, spiritual awareness, productivity, language capabilities, relationships and visual capabilities. Further, users also reported reduced anxiety, depression and addiction and pain relief. In a recent survey by Anderson and colleagues (2018), users also noted drawbacks such as illegality, stigma, physical discomfort, anxiety, overstimulation, cognitive interference, emotional difficulty and uncertainty of effect (Anderson et al., 2018). All of these reports are confounded by the lack of certainty relating to the actual dose used, or indeed the provenance of the active ingredient, and the absence of placebo conditions. For a recent review of past research with psychedelic microdosing, please see Passie (2019).

Question 4: Are there any relevant preclinical studies?

We found only two preclinical studies involving microdosing (Cameron et al., 2019; Horsley et al., 2018). Horsley and colleagues (2018) investigated the effect of microdosing on anxiety using an elevated plus-maze and observation of ecological behaviours. They defined a microdose of psilocin as 0.05 mg/kg, which equates to 3.5 mg for an average 70-kg human. Rats received three dosing sessions over 6 days with the last dosing session on the 6th day. Anxiety profiles were measured in Wistar rats 2 days after the final dosing session. Ethological behaviours including rears, head dips and stretch-attend were also measured during this period. Psilocin at 0.05 mg/kg significantly reduced entries into open arms, suggesting that microdosing may have an anxiogenic effect. This effect was not replicated in the ethological measures. Although the authors conclude that these results might have implications for future therapeutic applications, as they produce counter-productive behaviour, one obvious limitation is the interspecies scaling issue (Sharma and McNeill, 2009). It is questionable whether doses administered to animals translate to humans and the authors also acknowledged that the translational value of their results needs to be determined in a therapeutic context.

Cameron and colleagues (2019) tested the effect of repeated low doses of DMT in rats. They gave a dose for 2 months every third day and assessed behaviour with a broad range of tests. In a cued fear extinction learning test, they showed that animals froze significantly less than a control group, suggesting that DMT facilitates fear extinction memory. In the forced swim test, an antidepressant-like effect was observed. No change was observed in dendritic spine density in the layer V pyramidal neurons, and no changes were observed in gene expression (EGR1, EGR2, ARC, FOS, BDNF and 5HT2A). However, an impact on metabolism was observed in male rats; the weight increased by 182%, compared to 165% with vehicle (Cameron et al., 2019). Comparable to the Horsley et al. (2018) study, the interspecies scaling is a point of discussion together with the question of whether a short-acting substance such as DMT would show beneficial effects in humans without administration of a monoamine oxidase (MAO) inhibitor. Lastly, it should be emphasized that there is a need to conduct more research on long-term effects in order to assess the long-term safety of repeat doses.

Question 5: What is the pharmacology of psychedelics when used in microdoses?

The pharmacology of psilocybin and psilocin is still unclear due to the rapid decline in psychedelic drug research following their being made Schedule 1 drugs in 1968 (Rucker et al., 2018). This decline predated the growth of modern neuropharmacology. Thus, more research is required to build a more complete pharmacological profile of psilocybin and psilocin.

Psilocybin (3[2-(dimethylamino)ethyl]indol-4-ol dihydrogen phosphate ester; *O*-phosphoryl-4-hydroxy-*N,N*-dimethyltryptamine) belongs to the indolealkylamine class of psychoactive compounds (Table 2). It is an indole prodrug characterised by a 4-substituent, a phosphate group (Repke et al., 1977), six hydrogen bond acceptors and low lipophilicity (Geiger et al., 2018). Low lipophilicity may contribute to the notion that psilocybin does not cross the blood–brain barrier (Rautio et al., 2008).

In vivo, however, the majority of the prodrug psilocybin is rapidly converted to psilocin by alkaline phosphatases present in the blood and tissues. Psilocin has fewer hydrogen bond acceptors in its structure, which increases lipophilicity. In addition, NMR spectral studies have implicated an intramolecular hydrogen bond in psilocin that reduces the basicity of psilocin, increases its lipophilicity and also may render it stable to the action of MAO (Migliaccio et al., 1981). Following systemic circulation, psilocin is metabolized by either phase I or phase II metabolism (Figure 1). The former involves an oxidation reaction to form 4-hydroxyindole-3-acetaldehyde followed by either an oxidation to 4-hydroxyindole-3-acetic acid or a reduction to 4-hydroxytryptophole. It is believed that none of these metabolites are biologically active. The latter pathway involves the formation of a psilocin *O*-glucuronide conjugate through small intestine and liver enzymes UGT1A10 and UGT1A9, respectively. There is evidence that to some extent, glucuronidated psilocin can be converted back to psilocin (Brown et al., 2017). Although more than 80% of psilocin undergoes phase II metabolism, both phase I and II metabolites are ultimately eliminated through renal excretion.

Depending on body weight, the minimum active oral dose of psilocybin is approximately 4 to 10 mg in humans (van Amsterdam et al., 2011). Onset of action as defined by the first appearance of acute psychological symptoms begins 20 to 60 minutes following oral ingestion and 10 to 40 minutes following buccal administration (Geiger et al., 2018) and almost immediately following i.v. injection (Carhart-Harris et al., 2012).

Psilocin begins to appear in the plasma approximately 25 minutes after oral dosage, with peak levels reached after approximately 105 ± 37 minutes (Brown et al., 2017). A typical user responds to a full active dose for approximately 4 to 7 hours. Even a VLD can produce responses for up to 6 hours after dose administration (Hasler et al., 2004).

Table 2. The physical and chemical properties of psilocybin.

Name	Psilocybin
IUPAC name	3[2-(dimethylamino)ethyl]indol-4-ol dihydrogen phosphate
Other common name	4-Phosphoryl-*N,N*-dimethyltryptamine
Chemical formula	$C_{12}H_{17}N_2O_4P$
Molar mass	204.27 g/mol
Melting point	173 to 176°C (343 to 349°F)
Physical form	Solid
Soluble in	Water Saline

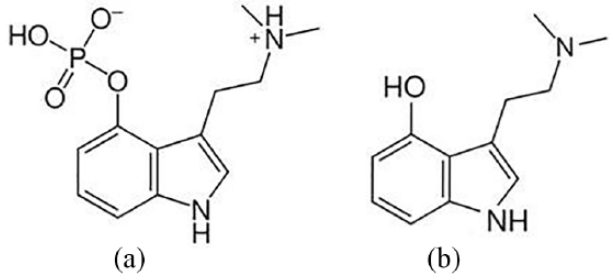

Figure 1. The structure of (a) psilocybin and (b) psilocin.

Question 6: Is microdosing safe?

Preclinical studies to assess the safety of repeated doses of psilocybin in rodents have not been conducted. That may be due to several factors, including the historical background of psilocybin as an ingredient in magic mushrooms that had been used in many cultures without apparent harm. Evidence from these accounts demonstrates a lack of serious adverse events resulting from psilocybin administration. There are, however, several non-clinical investigations of psilocybin's safety profile. The risk of an adverse cardiovascular event due to hERG (human ether-a-go-go-related protein) potassium channel blockade is low, with hERG assay results demonstrating minimal effect of psilocybin at concentrations up to 1000 μM (nominal) and completely without effect at 100 μM. That means that unwanted cardiac chronotropic effects with microdosing are very unlikely as the maximum plasma concentration of psilocybin produced by a 25-mg dose would not reach 160 nM (Brown et al., 2017).

Other potential and serious adverse events are cardiac valvulopathies due to repeated activation of serotonin 5-HT_{2B} receptors, which psilocin activates along with many other serotonin receptors. Several drugs have recently been pulled from the market due to this concern. The first example of this was the diet medication Phen/Fen, which had an unacceptably high fatality rate due to its effects on 5-HT_{2B} receptors in the heart (Connolly et al., 1997). Another example is methysergide, an ergot-derived prescription drug that is still being used today as a prophylaxis in difficult to treat migraine and cluster headache (MacGregor and Evers, 2017). It has a known risk of increasing cardiac valve dysfunction (Joseph et al., 2003). In early reports it was shown that although aortic insufficiencies disappeared in most cases after arrest of the methysergide therapy, the mitral insufficiencies remained unchanged (Graham, 1967). It remains to be seen whether repeated low-dose psilocybin administration in preclinical studies might produce valvular hyperplasia, and whether or not this would translate to the human user population. This concern is discussed more in the next section. So far psilocybin testing in preclinical studies has not revealed any signals of valvulopathy.

A different psychedelic that is more often used for microdosing, LSD, has been examined in rodents after repeated dosing schedules similar to microdosing. Comparatively low doses of LSD administered every other day for several months were shown to produce persistent negative behavioural changes that lasted for at least several weeks to months after LSD administration was discontinued (Marona-Lewicka et al., 2011). These changes included increased aggression, scruffy appearance, anhedonia and hyper-reactivity. Analysis of gene expression in key cortical regions like the medial prefrontal cortex indicated that LSD produced alterations in genes enriched for schizophrenia and bipolar depression that lasted long after the drug was discontinued (Martin et al., 2014). Of note, here the interspecies scaling question arises, and it is disputable whether the (low) doses used in animals are comparable to those used by humans (Sharma and McNeill, 2009). Related to these preclinical findings, another primary safety concern for 5-HT_{2A} agonists is the potential for adverse psychological response in humans (Carhart-Harris et al., 2016; Johnston et al., 2010; Vollenweider et al., 1998).

The lethal dose of psilocybin in a single administration in 50% of animals tested (the LD50) ranges from 280 mg/kg in rats and mice to 12.5 mg/kg in rabbits (Usdin and Efron, 1972; Williams, 2013). Animals receiving a very HD of psilocybin (10 mg/kg) exhibit sympathetic system effects such as irregularities in heart and breathing rate as well as mydriasis, piloerection, hyperglycaemia and hypertonia (Cerletti, 1958). Similar central excitatory effects were seen after the administration of 2–4 mg/kg intraperitoneal psilocybin in rhesus monkeys (Horibe, 1974).

Question 7: What receptors will be involved in the activity of microdosed psilocybin?

Psilocin predominantly binds to serotonin receptors: 5-HT_{1A}, 5-HT_{1D}, 5-HT_{1E}, 5-HT_{2A}, 5-HT_{2B}, 5-HT_{2C}, 5-HT_5, 5-HT_6 and 5-HT_7 (Table 3) (McKenna et al., 1990) and the serotonin transporter and partially to the norepinephrine transporter, similar to MDMA (Rickli et al., 2016). Hill slope values demonstrate that psilocin binds independently at all 5-HT receptors except 5-HT_{2B} where cooperative binding is exhibited (McKenna et al., 1990).

Cerebral 5-HT receptors that can be stimulated by psilocin are highly distributed among different regions (Table 3). Many behavioural and neuropsychological effects claimed to be elicited by microdosing are known to be modulated by these receptors (Anderson et al., 2018).

Psilocin acts as a partial agonist at the 5-HT_{2A} receptor with 46% (+/−2.4) response compared with the response produced by serotonin for signalling through the phospholipase C (PLC) pathway (Kurrasch-Orbaugh et al., 2003). It has a lower binding affinity to the 5-HT_{2A} receptor compared to LSD (Rickli et al., 2016). Currently there is only one study of the in vivo cerebral

Table 3. An overview of 5-HT receptors that are stimulated by psilocin. Ki values are based on displacement of an antagonist radioligand.

Receptor type	G-protein	Distribution	Physiological response	Behavioural response	Agonist	Antagonist	Drug classes that act on this receptor	Psilocin binding affinity: Ki (nM) (Halberstadt and Geyer, 2011)
5-HT_{1A}	Gi	Cerebral cortex, hippocampus, septum, amygdala and raphe nucleus in high densities. Low amounts also exist in the basal ganglia and thalamus (Beliveau et al., 2017)	I. Hypotension II. Increase DA release in the medial prefrontal cortex, striatum and hippocampus	I. Decreased anxiety and depression (Campos and Guimarães, 2008) II. Impairment of declarative and non-declarative memory III. Decreased aggression and impulsivity IV. Inhibition of drug-seeking behaviour	8-OH DPAT, buspirone, 5-CT (Barnes and Sharp, 1999), psilocybin (Mckenna et al., 1990)	WAY 100135 (methiothepin nonselective) (Barnes and Sharp, 1999)	I Analgesics (agonists) II Antidepressants (post-synaptic receptor agonists and pre-synaptic autoreceptor antagonists) III Anxiolytics (antagonists)	567.4
5-HT_{1D}	Gi	Trigeminal sensory neurones including peripheral and central projections to dural blood vessels and to the medulla (Longmore et al., 1997)	Inhibition of adenylyl cyclase	I. Modulates locomotion and anxiety II. Migraine prophylaxis (Longmore et al., 1997)	Dextromethorphan, sumatriptan, L694247, 5-CT (Barnes and Sharp, 1999), psilocybin (McKenna et al., 1990)	Sumatriptan, GR 127935 (metergoline, methiothepin nonselective) (Barnes and Sharp, 1999)	I. Triptans (agonists used for migraine)	36.4
5-HT_{1E}	Gi	High levels in olfactory bulb glomeruli and molecular layer of dentate gyrus. Low amounts in the adventitial layer of cerebral arteries (Klein and Teitler, 2012)	Inhibition of adenylyl cyclase		5-HT (Barnes and Sharp, 1999), psilocybin (McKenna et al., 1990)	None (methiothepin weak) (Barnes and Sharp, 1999)		N/A
5-HT_{2A}	Gq/11	High concentrations on the apical dendrites of pyramidal cells in layer V, neocortex (mainly prefrontal, parietal and somatosensory cortex) and the olfactory tubercle, as well as cardiovascular system (Beliveau et al., 2017)	I. Vasoconstriction II. Platelet aggregation III. Bronchoconstriction IV. Anti-inflammatory	I. Modulates addiction II. Increased anxiety III. Increased appetite IV. Improved cognition (learning and memory) V. Decreased sleep VI. Modulates sexual behaviour	Alpha-methyl-5-HT, DOI (Barnes and Sharp, 1999), psilocybin (McKenna et al., 1990)	Ketanserin, pimvanserin, pirenperone (Barnes and Sharp, 1999)	I. Atypical antipsychotics (antagonists) II. Antidepressants and anxiolytics (antagonists)	107.2
5-HT_{2B}	Gq/11	Predominantly peripheral, widespread tissue distribution including liver and kidneys (Julius et al., 1990)	Vasoconstriction	I. Regulates sleep (Qian et al., 2017) II. Increased GI motility, especially small intestine III. Increased cardiac hypertrophy in mice	Alpha-methyl-5-HT, DOI (Barnes and Sharp, 1999), psilocybin (Mckenna et al., 1990)	SB 200646 (also 5-HT_{2C} antagonist)		4.6
5-HT_{2C}	Gq/11	Mainly in choroid plexus, high concentrations in hippocampus, anterior olfactory nucleus, substantia nigra, amygdala, subthalamic nucleus and lateral habenula (Julius et al., 1990)	I. Vasoconstriction II. Increase phosphoinositide turnover	I. Increased anxiety II. Increased GI motility III. Modulates locomotion IV. Modulates mood and sexual behaviour	Alpha-methyl-5-HT, DOI, psilocybin (McKenna et al., 1990)	Mesulergine (also 5-HT_{2A} antagonist)	I. Antidepressant (antagonists) II. Orexigenic (antagonists) III. Anorectic (agonists) IV. Antipsychotic (agonists)	97.3
5HT_{5A}	Gi/Go	High concentrations in olfactory bulb and medial habenula of wild-type mice. Lower densities in neocortex, hippocampus and trigeminal nucleus	N/A	I. Modulates locomotion II. Increases sleep	5-CT, valerenic acid (partial agonist)	Methiothepin, ritanserin, asenapine, psilocybin (McKenna et al., 1990)	N/A	83.7
5-HT_{6}	Gs	Predominantly in the caudate nucleus, with lower concentrations in hippocampus and amygdala. Very low levels of expression in the thalamus, subthalamic nucleus and substantial nigra (Yoshioka et al., 1998)	Activation of adenylyl cyclase (HEK 293 cells)	I. Increased anxiety II. Reduced cognition and memory III. Negative effect on mood	EDMT, EMD-386,088	Amitriptyline aripiprazole, MS-245, psilocybin (McKenna et al., 1990)	I. Antidepressants (antagonists) II. Anxiolytics (antagonists) III. Nootropics (antagonists) IV. Anorectics (antagonists)	57.0
5-HT_{7}	Gs	Predominantly the caudate and putamen nuclei, the pyramidal layer of the CA2 field of the hippocampus, the centromedial thalamic nucleus and the dorsal raphe nucleus (Ruat et al., 1993)	I. Activation of adenylyl cyclase (HeLa cells and COS cells) II. Vasoconstriction	I. Increased anxiety II. Decreased mood III. Reduced working and reference memory	5-CT, 8-OH-DPAT, aripiprazole, AS-19, psilocybin (Glennon, 2003)	Methiothepin, mianserin, SB-269,270	I. Antidepressants (antagonists) II. Anxiolytics (antagonists) III. Nootropics (antagonists)	3.5

5-HT_{2A} receptor occupancy produced by the psilocybin metabolite psilocin in humans. That was done by the Copenhagen group led by Knudsen who used the PET tracer [^{11}C]Cimbi-36. This tracer is an agonist of the 5-HT_{2A} receptor and therefore particularly sensitive to displacement by another agonist, psilocin. Having performed a dose-finding study of psilocybin that ranged from 3 to 30 mg p.o. per person, they found that the plasma concentration that produced a 50% occupancy of the 5-HT_{2A} receptor was 1.95 (range 1.16–3.15) μg psilocin/L (Madsen et al., 2019). They also found that plasma psilocin was positively correlated with subjective intensity ratings and that doses producing less than 20% occupancy (i.e. probably less than 0.028 mg/kg body weight) were not detectable either by psychological or physiological measurements (Madsen et al., 2019), suggesting that this concentration might represent the threshold for microdosing, based on brain 5-HT_{2A} receptor occupancy.

At this dose level, several 5-HT receptors other than the 5-HT_{2A} receptor may also be affected. This could include antagonist activity at the 5-HT_6 and 5-HT_7 receptors that may improve mood and cognition (Ballaz et al., 2007; Mnie-Filali et al., 2009). The 5-HT_7 receptor is also implicated in the regulation of circadian rhythms (Lovenberg et al., 1993). Upon assessing binding affinity of LSD and DMT at 5-HT_7 receptors, similarly high K_i values of 9.5 nM (Ruat et al., 1993) were found. Additionally, it has been found that 5-HT_7 receptor activation reduces secondary hypersensitization in response to capsaicin in mice (Brenchat et al., 2009). Thus, psilocybin agonist activity at 5-HT_7 may relate to the ancient use of 'teonanacatl' to ease rheumatism.

Further, psilocin also binds with relatively high affinities to 5-HT_{1D} (K_i = 36.4 nM) and 5-HT_{2B} (K_i = 4.6 nM) receptors. 5-HT_{1D} is predominantly expressed in the trigeminal system, which may account for the recent reports of self-medication using microdoses of psychedelics to produce migraine prophylaxis (May, 2018). With regard to the 5-HT_{2B} there are concerns of the development of cardiac valvulopathy associated with agonism at 5-HT_{2B} (Elangbam et al., 2005). It is mostly the use of intermittent high-dose psilocybin intake that has been discredited. However, even with repeated microdosing there is a possibility that 5-HT_{2B} receptors might be stimulated enough to lead to tissue overgrowth. A potential mitigation against this risk is the suggestion that the efficacy of psilocin (EC50 > 20 μM) (May, 2018) is lower than that of 5-HT. Nonetheless, because psilocin also has a higher affinity for the 5-HT_{2B} receptor than 5-HT, further investigation is needed to understand better the risks associated with microdosing.

Some stimulation at 5-HT_{1A} receptors may also occur. Such activity has been implicated in the mechanism of action of antidepressant medications including SSRIs (Celeda et al., 2013). Activation of these receptors by psilocin could conceivably be involved in reduction in anxiety and increased mood swings (Carhart-Harris and Nutt, 2017) due to dense distribution of the receptor in the midbrain, limbic and cortical regions that regulate stress and emotion.

Question 8: Are the claims of the benefits of microdosing biologically plausible?

There have been only a few studies on the basic neurobiology of psychedelics at the 5-HT_{2A} receptor. Recent work has shown that psychedelics like DOI and LSD directly produce transcriptional activation of Immediate Early Genes (IEGs) like *cfos* in only about 5% of neurons within key brain structures, and that these activated Trigger Population neurons express significantly higher levels of receptor than the non-activated neurons (Martin and Nichols, 2016). Transcriptional activation of IEGs within neurons is generally accepted to be a reliable marker for neural activity (Joo et al., 2016). Further, psychedelics also act on subsets of inhibitory neurons, and non-neuronal cells like glia and astrocytes (Martin and Nichols, 2016). Together, these data indicate that within specific brain regions, psychedelics trigger complex patterns of excitatory and inhibitory neurons in small subsets of cells, and that how these cells are activated differs between brain regions (Martin and Nichols, 2016).

Genes acutely activated by LSD in the brain are predominantly involved in synaptic plasticity (Nichols and Sanders-Bush, 2002; Nichols and Sanders-Bush, 2004). Accordingly, activation of 5-HT_{2A} receptors in brain slice culture modulates aspects of long-term plasticity, and expression of brain-derived neurotrophic factor (BDNF) (Vollenweider and Kometer, 2010). BDNF expression is also observed to increase in primary cultures of cortical neurons 24 hours following the application of psychedelics (DOI, DMT, LSD) (Ly et al., 2018). Blockade of the receptor for BDNF, Trk-B, prevents increased spinogenesis and synaptogenesis in cortical neurons that have been treated with psychedelics. Interestingly, the mammalian target of the rapamycin (mTOR) pathway is activated downstream of psychedelics in cortical neuron cultures similarly to ketamine, and likely mechanistically underlies the synaptogenesis (Ly et al., 2018). None of these preclinical studies, however, utilized psilocybin, and it remains to be seen if it produces the same effects, and if so, at what dose?

Psychedelics are known to induce behavioural tolerance, an absence of behavioural effects after repeated intake of a substance. Previously it was shown that behavioural effects were for example diminished after repeated doses of LSD (Abramson et al., 1956); in addition, another study showed these effects to be associated with reduced cortical 5-HT_{2A} receptor binding (Gresch et al., 2005). Serotonin syndrome-related symptoms, skin jerks, shaking behaviour and hyperthermia, induced by a single dose of the 5-HT_{2A} agonist DOI in rats were absent after repeated low dosing, suggesting behavioural tolerance (Pranzatelli and Pluchino, 1991). Although speculative, this downregulation of the 5-HT_{2A} receptor might be a mechanism of action underlying some of its putative therapeutic effects. An example is obsessive-compulsive disorder (OCD), a psychiatric condition that is characterized by increased 5-HT_{2A} binding (Adams et al., 2005). Preliminary data have shown that administration of low to high doses of psilocybin lead to symptom reduction in patients with OCD (Moreno et al., 2006). It was previously suggested that a re-balance between 5-HT_{1A} and 5-HT_{2A} receptors might be responsible for observed therapeutic actions (Buchborn et al., 2014), but this remains to be investigated.

In peripheral tissues, very low doses of psychedelics have profound anti-inflammatory effects (Yu et al., 2008). In general, psychedelics in the phenethylamine class such as DOI have more potency than those in the ergoline class such as LSD. In a rodent model of asthma, for example, levels of the R stereoisomer (*R*)-DOI that are 30 times lower than the behavioural threshold can have profound effects to prevent inflammation, T-Helper Cell Type 2 (Th2) cell recruitment, eosinophilia and mucus production in the lung,

resulting in animals that can breathe normally after exposure to an allergen (Nau et al., 2015). In another animal model of inflammatory bowel disease, levels of the psychedelic (*R*)-DOI 30 times lower than the behavioural threshold nearly completely prevented intestinal inflammation (Nau et al., 2013). It remains to be seen whether very low levels of psychedelics are also anti-inflammatory in humans, and if the anti-inflammatory activity also occurs in the brain, but if these findings do translate then levels typically used in microdosing regimes for some psychedelic compounds would be predicted to have significant and beneficial anti-inflammatory effects. Interestingly, although LSD is one of the most powerful and potent mind-altering psychedelics, it is comparatively among the least potent anti-inflammatories tested (Yu et al., 2008).

Question 9: What is the legal position of microdosing?

The answer to this question is complex due to differences in national regulations. In general, under the UN Conventions, LSD and related compounds, psilocybin and DMT are controlled as Schedule 1 drugs – i.e. are defined as being the most harmful and as having no medicinal value. In other words, they are subject to the most extreme restrictions and penalties for unapproved possession. These constraints apply to any dose of the drug, even a sub-psychoactive or microdose level. Research can be carried out with the right ethical regulatory and institutional approvals, but dosing would have to be conducted in a secure environment like a hospital or research ward. For repeated microdosing, this adds significant costs and complexity to any study, which is likely why none have yet been reported.

However, this situation is easing for psilocybin as a result of several successful clinical trials in recent years, and both the European and US regulators have given approval for studies (NIH, 2018) with psychedelic doses of synthetic psilocybin made to GMP standards. That means that microdosing trials of similarly sourced product for clinical therapy are likely also to be approved, though as yet we do not believe any have been submitted.

Question 10: What are the regulatory issues?

Unfortunately, due to their long history of anecdotal use in recreational settings, none of the psychedelics has ever followed the conventional drug research and development path expected by contemporary standards. Thus, at best, doses have been selected based on published data in a variety of indications but mostly to provide an indication for an upper safety limit. In a pooled analysis of psilocybin Studerus et al. (2011) classified active oral doses within a vast range of about one order of magnitude difference, between 0.045 and 0.315 mg/kg, which translates into 3.15 to 22.05 mg for a 70-kg human (Studerus et al., 2011). Such a range is quite surprising for active principles with the pharmacological potency of psychedelics. Given such underdetermination, regulatory standards will most likely require dedicated dose-finding studies (more than one) to provide a rationale explaining the known individual differences that have been reported in the clinical response to treatment and most importantly, the dose chosen for late development. In this context, the information provided from oral dosing, resulting plasma psilocin levels and corresponding brain 5-HT_{2A} receptor occupancy will turn out to be informative.

Parallel fixed dose designs are usually recommended (ICH, 1994). In some cases, four arm range studies could be necessary; under these circumstances microdoses could be used to test pseudo-placebo properties or alternatively a peculiar pharmacological activity.

Another issue pertains to the limited pharmacokinetic data available in order to evaluate a dose-concentration–response relationship for psychedelics. Updated ADME studies are not available for psychedelics, although the characterization of their metabolites and their role in the active principle efficacy or safety profile might prove relevant to interpret and predict their clinical effect. Once pharmacokinetics of the parent compound and its metabolite(s) are established, variation of clearance if any, its prediction by body weight and the concentration–response relationship for the claimed clinical effect must be presented. If possible, biomarker(s) (e.g. single-nucleotide polymorphisms (SNPs)) at the 5-HT receptor subtypes where they have affinity should be linked to the risk/benefit profile and thus to the therapeutic effect, and they could be used to enrich/stratify the population of interest. Because psychedelics have been reported by some to possess a large inter-individual sensitivity, the definition of a precise concentration–response relationship may be difficult to demonstrate, especially once a microdose range is reached.

Question 11: What are the future research needs?

Microdosing is generally accepted as the use of a functionally low dose of a psychedelic compound over multiple dosing sessions with the intention of improving mental and physical well-being, cognition or creativity (Fadiman, 2011; Johnstad, 2018). A systematic study of microdosing psychedelics investigated by means of observation changes in psychological variables of microdosers. Small changes in a sub-set of variables were found, i.e. decreased depression and stress, decreased mind wandering, increased absorption and increased neuroticism. Interestingly, these variables were not those that participants most expected to change, suggesting that long-term changes may be due to biological changes and not only expectations (Polito and Stevenson, 2019). Nonetheless, the possible effects and implications of microdosing remain largely unknown. Although there is a large database of reported effects of 'microdosing' on online fora, the true amount of active substance in these is unknown as are the peak plasma psilocin concentrations achieved during 'intoxication'. Further, while in these anecdotal reports the user deliberately ingests a substance for a reason, expecting positive effects, it is difficult to distinguish between expectation 'placebo' effects and the effect of a microdose. These non-pharmacological effects, described as set and setting, are also known to be of influence when taking a full dose of a psychedelic (Hartogsohn, 2017). Another unknown is whether effects are noticeable after only one microdose or that a certain 'build-up' is needed, supported by underlying neurobiological changes, before effects occur.

Therefore, rigorous placebo-controlled clinical studies need to be conducted with different low doses of the drug to determine whether there is any evidence for the claims being made by microdosers. The types of cognitive testing performed should include several different validated psychological instruments and preferably cover the concepts mentioned in the Research Domain Criteria (Cuthbert and Kozak, 2013), and not simply rely on

anecdotal accounts or simple tests. Generated knowledge in healthy volunteers will provide clear information on which cognitive aspects can be enhanced with microdosing. This knowledge will provide a first hint as to whether microdosing can be of value in the treatment of specific symptoms in psychiatric populations. Anecdotal reports suggest, for example, that microdosing might help in combatting attention deficit hyperactivity disorder (ADHD) symptoms; studies including measures related to symptom domains like executive functioning, attention and temporal processing will help to decode the potential of microdosing as a therapeutic agent. In terms of biological mechanism of action, more (pre)clinical work needs to be performed to understand fully the complex interaction of different cell types, and their responses to psychedelics at the molecular level such as elucidating peripheral or central signalling pathways involved, if any, in the process of microdosing (Kuypers, 2019). Resulting findings can provide theoretical grounds for why microdosing could work in alleviating cluster headache in patients suffering from it (Anderson et al., 2018; Johnstad, 2018).

Whereas most anecdotal reports focus on the positive experiences with microdosing, future research should investigate the molecular mechanisms behind low-dose psilocybin behavioural effects as well as address potential risks of (multiple) administrations of a psychedelic in low doses. Although extensive toxicology has been conducted on a single active dose of psilocybin and has been proven to be safe (Brown et al., 2017; Johnson et al., 2018), further research is required to understand better the possible health risks incurred by microdosing, especially in relation to cardiac and lung tissue. These studies would involve (pre)clinical safety and tolerability tests of multiple low/microdoses of psilocybin over an extended period of time. To that end, continuous monitoring of physiological parameters including heart functioning in addition to assessment of receptor turnover at low/microdoses as well as receptor occupancy will shed light on the potential negative consequences microdosing could have.

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Microdosing psychedelics: Too much hype, almost no rigorous research

A call to explore microdosing's psychological effects and therapeutic potential within psychiatry

Stephen Ross

This timely article ('Microdosing psychedelics: More questions than answers? An overview and suggestions for future research') provides an excellent overview on the topic of microdosing psychedelics. The review focuses predominantly on psilocybin with some mention of other psychedelics (i.e. LSD, ibogaine and DMT). This article is organized around a series of questions and answers that includes the following topics related to microdosing: basic definitions, varying dosing regimens, relevant preclinical data, pharmacology, safety issues, potential biological mechanisms of action, scientific evidence base (or relative lack thereof) from published peer-reviewed research, legal and regulatory issues, and a call for rigorous placebo-controlled trials to test the various beneficial claims of microdosing made so far by anecdotal reports.

The therapeutic application of the classical psychedelics within psychiatry has made a historic come back within the last two decades and is at inflection point with a growing body of rigorously conducted research pointing to the promising clinical utility of psychedelic-assisted psychotherapies to treat a range of psychiatric disorders, with the data most robust for: cancer-related psychological and existential distress (Gasser et al., 2014; Griffiths et al., 2016; Grob et al., 2011; Ross et al., 2016), alcohol and tobacco addiction (Bogenschutz et al., 2015; Johnson et al., 2014), and major depression (Carhart-Harris et al., 2016; Osorio et al., 2015). The doses used in all of these clinical trials are of the 'macro' variety, typically consisting of moderate to high-dose psilocybin, administered as part of the psychedelic therapy model in combination with psychotherapy with the goal of inducing significant alterations of consciousness, including mystico-mimetic states (Bogenschutz and Ross, 2018).

In contrast, and as defined in this article, microdosing is a practice of consuming very low doses of a psychedelic substance (that produce acute drug effects that are either not perceptible or minimally identifiable), utilizing a repeated dosing regimen, and with the goal of improving well-being, enhancing productivity or increasing creativity. It is distinct from both psychedelic therapy (i.e. using high doses of psychedelics to occasion mystical-type experiences, and used historically to treat conditions such as alcoholism and terminal cancer-related existential distress) and psycholytic therapy (i.e. using lower doses of psychedelics to produce perceptible and significant shifts in cognition and affect to enhance psychotherapy, historically used in combination with psychoanalytic psychotherapy to treat various psychiatric conditions such as anxiety spectrum disorders) (Ross and Bogenschutz, 2017). Structured microdosing regimens employed so far (typically by lay individuals with the intention of receiving some positive benefit) range from daily use to dosing every 3 days (Fadiman, 2011), and occurring over varying time-frames from monthly to ongoing. Microdosing has surged in popularity over the last several years and has been associated with the use of serotoninergic psychedelics (i.e. LSD, psilocybin, ayahuasca, iboga), cannabinoids (i.e. CBD), and dissociative anaesthetics (i.e. ketamine) (Kitchens, 2018). Even though microdosing does not cause significant alterations in perception with acute administration, it has led to numerous anecdotal reports (featured in a rapidly growing number of media articles) of claimed benefits in a variety of domains including: Psychological (i.e. improved mood, energy, emotional balance, empathy, openness, introspection; decreased pain and alcohol/drug use or craving); Cognitive (i.e. improved focus, concentration, mental clarity); Creativity (i.e. improved idea generation and divergent thought processes); Spirituality (i.e. improved meaning in life); Interpersonal (i.e. improved connectedness, sensitivity to others, relational skills); and General well-being and quality of life (i.e. improved sleep quality, healthy eating habits, sexual function) (Austin, 2016; Kitchens, 2018).

Despite all of the growing interest and purported claims of benefits of microdosing, basic knowledge about microdosing, including therapeutic effects, is virtually absent due to almost no peer-reviewed publications stemming from rigorously conducted research. Some of the most significant and important gaps in the knowledge base of microdosing include the absence or paucity of: rigorous design methodology including randomization, placebo control, adequate blinding integrity, and the use of appropriate inclusion/exclusion criteria to minimize potential harm; prior approval with appropriate ethical and human subjects review boards; the use of and dispensation of an exact known dose of pharmaceutical grade psychedelic in a controlled setting; understanding basic effects on psychological, cognitive and affective domains; adequate safety monitoring and knowledge of acute or long-term safety issues; understanding of basic neurobiological or potential mechanisms of action, such as neuroimaging (i.e.

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PET, functional MRI), physiological data (i.e. EEG, MEG) and biomarkers (i.e. BDNF).

This article touches on most of these gaps. The review article points out that there has only been one published trial that specifically examined the effects of psilocybin microdosing. This was an open-label, non-controlled trial, with uncertain doses of psilocybin ingested, that was conducted without ethical approval. It reported on improvements in two creativity-related problem-solving tasks following recreational psilocybin microdosing (Prochazkova et al., 2018). A limitation of the present article is the focus on psilocybin even though online fora suggest that recreational LSD microdosing may be as common (if not more so) than psilocybin microdosing (www.reddit.com, 2019). By not focusing equally on LSD microdosing, the article does not capture the most rigorously conducted and peer-reviewed published trial of microdosing to date. Unlike all of the prior publications on microdosing, this trial was approved by an independent ethics committee, included random assignment, double-blind methodology, and the use of a placebo condition (Yanakieva, 2019). Further, appropriate inclusion/exclusion criteria were used to enhance safety, the trial was conducted in a monitored inpatient setting to optimize safety and exact doses of pharmaceutical grade cGMP LSD were administered. In comparing three microdoses of LSD (5, 10 and 20 μg) to placebo, the trial reported that LSD microdosing produced temporal dilation in the absence of significant consciousness alteration (Yanakieva et al., 2019).

The review article also focuses on some theoretical safety concerns such as the link between 5-HT_{2B} agonism and cardiac valvulopathies (Cavera and Guillon, 2014). The article would have been strengthened by a call to monitor broadly for potential adverse medical and psychiatric effects in future microdosing research to be able to identify all of the unknown risks that may be associated with microdosing. For example, we do not know the risks associated with the interaction between microdosing and underlying psychiatric illnesses. All of the modern therapeutic trials of psychedelic-assisted psychotherapies exclude participants with psychotic spectrum illnesses because of the known negative association between psychedelic use and psychotic exacerbation in those with underlying psychotic illness (Ross and Peselow, 2012). In the early stages of microdosing research, it would be important to begin cautiously by excluding individuals with significant psychiatric, medical or neurological illnesses.

One area not covered by the review article is speculation on the potential therapeutic utility of microdosing within psychiatry. If some of the claimed psychological or cognitive benefits (i.e. improved mood and attention; decreased substance craving and pain perception) of microdosing are real (i.e. not simply due to placebo or expectancy effects), the next logical step would be to test the potential efficacy of microdosing in various clinical populations (i.e. major depression, bipolar depression, ADHD, addictive disorders, pain disorders) through RCTs, and beyond through the drug development process. Funding sources would have to be considered, whether that would come through private philanthropy, pharma or governmental funding agencies (i.e. NIHR in Europe or NIH in the USA). Finally, if microdosing proves to be effective for the many claimed effects reported in the lay public (i.e. enhanced creativity, work productivity, learning, memory, empathy, connection to others, spirituality), it could potentially be used to improve function in 'normals' without specific disease states, although it is unclear how drug development would proceed for non-clinical entities by using mostly illegal substances.

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Psychedelics: What are low doses and 'microdoses'?

Matthias E Liechti

In clinical pharmacology, 'microdosing' refers to the use of a dose of a substance with <1% pharmacological activity to study pharmacokinetics (PK), including absorption, distribution, metabolism and excretion, potentially using non-good-manufacturing practice (GMP) material and/or radiolabelled substances (e.g. Muehlan et al., 2018). 'Microdosing' with lysergic acid diethylamide (LSD) or psilocybin refers to the use of low to very low doses (i.e. 5–20% of fully active doses; Table 1). I would rather label such use as 'low to very low doses'.

While I mostly agree with the views in the article, I would like to add some additional thoughts on dosing with a focus on LSD. What is actually meant by the micrograms of LSD doses? Correct doses are obviously unknown in the case of illicit sources, and the correct reporting of doses is also an issue in scientific publications. Research in the 1950s to 1970s used LSD tartrate, whereas modern research commonly uses LSD base (Liechti, 2017), with the exception of at least one study (Yanakieva et al., 2019). A dose of 100 µg LSD base corresponds to 123 µg LSD tartrate (when being free of crystal water or methanol solvate; Mesley and Evans, 1969) – this dose may not be considered low (Table 1). Thus, researchers need to indicate whether they are reporting base or salt doses. Additionally, LSD is mostly not a pharmaceutical product and not manufactured according to GMP with defined content and stability. Researchers produce their own formulations. It is often not reported where the substance was obtained from and the way in which it was formulated as the final study drug. This raises many questions. Are the reported doses salt or base? What is the purity? What is the content of crystal water, solvate and/or residual solvents? How was this factored into the reported dose? What is the content uniformity and stability of the product throughout the study duration? What is the amount of inactive iso-LSD in the pharmaceutical formulation?

LSD is inactivated to iso-LSD depending on temperature, solvent and pH and thus may be unstable in certain formulations. Other stress factors such as light, oxygen or tap water chlorine may also lead to decomposition of the LSD molecule. In fact, amounts of iso-LSD were detected in plasma in research subjects, indicating that approximately 30% of the LSD that was administered likely isomerized to inactive iso-LSD possibly within the LSD capsules that were used (Steuer et al., 2017). Novel PK studies (Holze et al. 2019) that use validly defined doses of a novel LSD formulation indicate that previous studies used 70 and 140 µg of LSD base (equivalent to 86 and 172 µg LSD tartrate) rather than the reported oral doses of 100 and 200 µg LSD base (Dolder et al., 2017; Liechti, 2017; Preller et al., 2017). In addition to correctly assessing and reporting the study drug, PK data are needed, thus providing the basis of the present discussion and any drug development. Plasma concentrations provide an objective measure of the substance that actually arrives in the body by accounting for dosing, bioavailability and inter-individual differences in absorption, distribution, metabolism and excretion. Plasma concentrations are also needed to compare formulations and substance exposures between different studies and different research groups and should be generated for each novel formulation.

With regard to 'microdosing with LSD', researchers cannot unequivocally conclude that 5–20 µg LSD base has no acute subjective effects or does not impair normal functioning as noted in the definition of 'microdosing'. I would argue that these doses can produce similar acute subjective effects but to a lesser degree compared with clearly psychoactive doses (> 25 µg LSD base). A recent placebo-controlled study that used single doses of 5–20 µg LSD tartrate (GMP-formulated, 4-16 µg LSD base) reported statistically significant acute subjective drug effects (Yanakieva et al., 2019). Studies that used PK-pharmacodynamic modelling (Dolder et al., 2015, 2017; Holze et al., 2019) allow the evaluation of plasma concentration/dose–effect relationships of LSD in humans, in which subjective effects parallel plasma LSD concentration–time curves. Plasma concentrations of LSD at the EC_{50} for 'good subjective drug ratings' are very low (1 ng/mL). Subjective mean good drug effects of 25% of these full doses have been reported at an average plasma LSD concentration of 0.4 ng/mL (Dolder et al., 2017; Holze et al., 2019). The C_{max} after 100 µg LSD base administration was 1.7 ng/mL (Holze et al., 2019). Based on the linear PK of LSD, C_{max} values of 0.4 ng/mL are likely reached with a 25-µg dose. Based on the available data and ongoing studies, base doses of LSD of 25, 10 or 5 µg can be postulated to produce approximately 25%, 10% and 5%, respectively, of the effects of a fully active dose of 100 µg LSD base. Additionally, there is no indication that the acute subjective effects of these very low to low doses of LSD are qualitatively different from a full dose. Thus, there is no apparent evidence that LSD, which impairs cognition at active doses, would magically enhance concentration when used at lower doses as described by users. In fact, decreases in self-reported concentration and task-measured cognitive performance have been reported at high and low plasma LSD concentrations (Dolder et al., 2016; Schmid et al., 2015). Very low to low doses of 5–20 µg LSD tartrate ('microdoses') did not significantly alter self-ratings of perceptual distortion or subjective concentration,

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but trends towards impairments were observed (Yanakieva et al., 2019). These effects would likely become significant in well-powered studies with larger sample sizes.

This raises another important issue. Very low doses of substances will produce very small effects. To validly assess small treatment effects, study sample sizes need to be larger than those that are common in experimental psychiatric research. Additionally, sensitive measures need to be used. Many validated psychiatric scales may not be sufficiently sensitive to detect small drug effects, and simple drug-effect visual analogue scale ratings are likely better. Furthermore, vital signs could serve as a simple objective measure of reactivity. However, psychiatric studies typically have shortcomings with regard to performing vital sign assessments. For example, very low to low doses of psilocybin did not alter blood pressure in one study (Hasler et al., 2004). However, for this finding to be valid, vital signs need to be assessed according to standard operating procedures. This includes the use of scaled instruments, exactly determined time points after drug administration, time-matched placebo control measures and so on. For example, a safety and efficacy study reported that LSD did not significantly alter blood pressure or heart rate at a dose of 200 µg LSD (Gasser et al., 2014). However, this same dose and lower doses were subsequently shown to significantly and relevantly increase blood pressure, heart rate, body temperature and pupil size in studies that used standardized measures (Schmid et al., 2015; Dolder et al., 2016).

Altogether, we are still in the incipient stage of modern research on psychedelics. Even for relatively high doses of these substances, the data are still scant and inconsistent. Thus, it is too early to make valid conclusions about the effects of very low doses of these substances. Currently (Passie, 2019), I see no valid data that indicate that LSD or psilocybin has either beneficial or adverse effects on health when used repeatedly at low to very low doses (Passie, 2019). This simply needs to be studied further.

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Commentary

James Fadiman and Sophia Korb

As microdoses are being used worldwide, this is a timely article. Prudently, the authors have focused on synthesized psilocybin, as it may soon become more available. As our own research has been entirely anecdotal, and although it includes reports from 51 countries and thousands of individuals, it does not answer any of the questions raised here. What our exploratory findings may have done is help raise the level of interest about the reported negative or positive effects and mechanisms of action. While we have added suggestions and noted a few concerns here, the investigations proposed in the article are all necessary and fundamental.

Early on, it could be important to determine if the same weight of psilocybin in a mushroom with its other alkaloids (found in over 100 mushroom species) has a similar behavioural profile to the synthetic. Equally useful, and perhaps eventually as necessary, would be to replicate the same study with LSD-25 and 1P-LSD. The reason for suggesting these equivalence studies is that of the several hundred thousand people known to have microdosed, less than 1% of them actually used the GMP grade psilocybin. If their experiences differ from those using the synthetic substance, a great deal of otherwise correlative data would need to be put aside.

It seems to us that the worry about cardiac valvulopathy is excessive, given the overall safety profiles of all of the classic psychedelics described in several of Dr. Nutt's publications.

The Fen-Phen experiences of heart valve disease development in the 1980s and 1990s inspired new research in identifying the specific 5-HT receptor subtype involved in drug-induced heart valve disease. In the cases of cardiotoxicity and Fen-Phen, both 5-HTP2A and 5-HTP2B are implicated. In fact, 'norfenfluramine was found to be two orders of magnitude more potent at 5-HT_{2B} and 5-HT_{2C} receptors compared with 5-HT_{2A} receptors' (Hutcheson, 2011). While we have some information about the affinity of LSD towards different receptors, we have little information about how its unique 'crystal structure' may result in different heart health outcomes (Wacker et al., 2017).

Affinity does not tell the whole story. The doses of Fen-Phen used in the 1980s and 1990s far exceed the doses used in microdosing, seemingly resulting in several orders of magnitude more *activity* at the receptors. Additionally, in the cases of heart valve disease in Fen-Phen, all of the patients were symptomatic. Of the thousands of people who microdosed, no one has reported any heart valve trouble during their period of microdosing, and many people have been microdosing for over a year. All the people we have surveyed with heart problems had them before they started microdosing.

The problem, and it is a very real one, is that this article will be reviewed and popularized over the many different psychedelic and general media sites with varying degrees of accuracy. Since it is highly unlikely that large-scale long-term research necessary to investigate this possibility will ever be funded, the concern will never be validated or disproved. There were a number of frightening scenarios raised about psychedelics during the earlier research era, about LSD in particular, none of which were ultimately verified. However, their wide circulation led to considerable and unnecessary fears among millions of individuals using these substances. We need be careful not to create such fears before we have evidence. Given the serious and multiple warnings given out with most prescription medicine, that there might be unknown side effects to microdoses is to belabour the obvious.

We would look for an expansion of the receptor research (Question 7). It would be a great gift to all psychedelic research if studies could begin to go beyond measuring 5-HTP2A receptors and include, at least, the mTOR and TrkB signalling pathways as well (Ly et al., 2018).

A question to investigate is how the well-described accelerated neural plasticity of a number of psychedelics at high doses is diminished or intensified through periodic microdosing. Early speculation by Kornfeld (Kornfeld and Fadiman, 2013) has now been artfully demonstrated by the work of Ly's group (Ly, et al. 2018). This seems to be an especially fruitful area, given the growing body of research linking neural plasticity with both mental illness and recovery.

We are encouraged that in Question 8, the authors went beyond 5-HTP2A receptors and looked at peripheral tissues with doses well below behavioural thresholds as well. We hope the number and kinds of physical systems evaluated for effects continue to expand. For example, although it is now generally accepted that the number of neurons that exist outside of the brain exceeds the number within it, psychedelic researchers have not yet developed research methods to measure changes in gut neurons due to the effects of psychedelics or how those changes affect human biology and behaviour.

Finally, the issues of dose and schedule remain critical. While many pharmaceuticals have a given activity and that more or less of a dose leads to more or less of the same activity, this is not true for psychedelics at higher doses and far less so for microdoses. One size does not fit all, so that the identical dose, however calculated, will not yield the same results across individuals. This may be a hard problem, especially given the few research models popular in pharmacology in general. As for the effects of multiple doses over time, there has never been a suggested protocol that did not include days without dosing, in contrast to almost all psychiatric medications that warn of potential serious health issues if even a single dose is missed. For this and other reasons, psychedelics do not fit neatly into much of current psychopharmacology and thus need to be researched.

Our few concerns aside, these research proposals are a major step forward for psychedelics in general and microdoses in particular.

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Commentary

Torsten Passie

Psychedelics and creativity

I would recommend not mentioning just these very few anecdotal cases in respect to creativity and psychedelics. There are some good studies and reviews about the subject (Hartmann, 1969) on 40 prominent painters at the German Max Planck Institute of Psychiatry in Munich and the review on the subject by Krippner (1985).

When it comes to the very few studies looking for low doses of psychedelics and creativity (review in Passie, 2019), no study revealed any significant/relevant effects under controlled scientific conditions (e.g. McGlothlin et al., 1967). The study of Prochazkova et al. (2018) claimed (under weakly controlled conditions in respect to dosing and environment) increased lateral thinking, which has been discussed as a marker of creativity. This study employed doses of psilocybin that were above the perceptible level (4–8 mg p.o.). However, increased lateral thinking does not mean that the drugged subjects have shown increased creativity in a valid sense, e.g. creating more original painting.

Definitions: Microdosing and minidosing

I do not agree with the authors' narrow definition, since it does not reflect fully what is used in the literature and the appropriate Internet entries. It has been proposed that the term 'minidosing' could be used to separate the approach of taking small perceptible doses. It is also clear that many authors and Internet entries suggest the practice of just taking one dose at a time rather than a few ones consecutively as, for example, seen with the Fadiman scheme. This is also valid for taking a tenth or a twentieth of a usual dose. However, the issues related to definitions point towards the question/definition of what is considered a 'full dose'. In the case of LSD, some authors reasonably argue that 150 µg is a full dose (especially in females), whereas others consider 250 µg a full dose. This is a significant issue, because 15 µg is usually not perceptible by most subjects, but a dose of 25 µg is for most subjects (as shown in some scientific studies). Therefore, the definition has to be sharpened before scientific consensus can be reached and the evidence from so-called microdosers disseminated on the Internet as well as studies of anecdotal evidence (e.g. Johnson, 2018), which suffers from such inaccuracies, can be taken seriously.

Dosing of dried mushrooms

Plant/fungal material is generally quite unreliable for calculating a dose. I do not agree with the author's statement that 3.5 g *P. cubensis* is 'a usual recreational dose'. Most recreational users take 1 to 2.5 g as a recreational dose, which is also recommended in most books in the field. From my experience, and the research studies of Abramson and Rolo (1967), I would state that a dose of psilocybin below 3 mg is below the perceptible range. Usually, doses above this level can become apparent. For example, Prochazkova et al. (2018) used 4–8 mg psilocybin, i.e. more than a microdose, thus, more consistent with the definition of what might be considered a minidose.

The most used dosing regime and effects of micro- and minidosing

It can be easily seen in Internet entries that most subjects who take microdoses recreationally for 'bettering performance' take doses that give them some perceptible effects. Even a microdosing proponent like Paul Austin recommends doses where you can feel/perceive some alterations to some extent. How would you better your performance if nothing can be felt from a dose?

Following my comprehensive research into this topic (Passie, 2019), I have never come across anything about a 'workaholic approach' (dosing during weekdays, but not on weekends) as suggested by the authors. This also does not make much sense form a pharmacological point of view, because tolerance to LSD develops very quickly. Be reminded, that the US military has dosed soldiers with increasing daily doses to try to make them 'immune' to LSD's effects (Ketchum, 2006).

I think that a minidose (e.g. 20 to 50 µg LSD), in contrast to a microdose (which I define as something below 20 µg LSD, e.g. 5–15 µg), makes a significant difference in terms of recreational as well as scientific studies as it definitely alters psychological functioning and the cognitive system.

However, this alteration is not in any way equivalent to stimulants like Ritalin or amphetamine as is sometimes reported anecdotally. It is more a dissociation from the environment and the person itself. Cognitive abilities have been proven to be compromised in

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many studies with LSD and psilocybin employing a very low dose range (Passie, 2019). It is also important to register these (potentially) distracting effects. There are also a few scientific reports of people who have been given very low doses of LSD for treating depressive mood. These had negative results with very few patients experiencing a small improvement.

What is plausible (and has been experienced by this author) is that a minimal sympathomimetic effect (for sure not compatible with any sort of usual stimulant!), which might be still there up to 20 hours after a 10- to 15-µg dose of LSD, can cause problems with falling asleep, especially in sensitive persons. It is of interest how long it takes following intake for effects to occur. One could think of a train of effects induced in the organism, which is pushed on and may influence the organism even after virtually all of the substance has left the organism.

I definitely do not see the Fadiman protocol (5–15 µg LSD every third day) as the most used approach. It might be viewed as the most widely known, but by far (!) the most 'microdosers' use one occasional dose, not a regular intake. This also makes it very questionable what effects can be/are felt or not, especially when it comes to taking 10 µg just a few times per year (which is apparently what most users do). As Fadiman's coworker on his more or less systematic Internet surveys, Sophia Korb has mentioned in a lecture (conference 'Beyond Psychedelics', Prague 2018) that they know of just three persons who have dosed regularly (according to the Fadiman protocol) for more than 3 weeks. These three subjects were terminal cancer patients and felt quite normal up to day 50. Between days 50 and 60 they all became much more psychologically labile, i.e. having larger mood changes (in the positive as well negative direction, with daily fluctuations), as measured using the PANAS scale.

To my mind, the study published by Horsley et al. (2018) does not have any seriously calculable implications for humans. Its limitations should be discussed.

Possible alterations of gene expression and receptor proteins

There are serious doubts that the repeated doses of LSD, which have been used in rodents, are comparable to microdoses in humans. I am not an expert on interspecies scaling, but, for example, (just by simplified arithmetic) the studies by Martin et al. (2014) have used doses which are 12,000 times higher than a microdose in humans. According to a recent review (Sharma et al., 2009), it appears not to be congruent with scientific data to state that the dose used by Martin et al. (2014) is in any way comparable to a microdose in humans. Therefore, to date we know nothing about possible changes in gene expression induced by regular LSD intake in humans.

I doubt that the gene/BDNF changes which were found with very high daily doses in animals can be scaled up to humans using microdoses every few days. Issues of adaption and tolerance should be discussed in this respect.

Receptors are proteins. These proteins and others might be altered by repeated intake of, e.g. LSD, even in very low doses (Buchborn et al., 2016). Even if this is somewhat speculative, it seems probable.

On the possible induction of cardiovascular valvopathy

In respect to a possible induction of cardiovascular valvulopathy by chronic 2-HT2R activation, it is worth mentioning that the studies of Bender and Sankar (1968) in the 1960s involved doses of 100 µg LSD for up to 35 months on a daily basis without any observable damage. However, their methods of investigation might not have been sensitive enough to detect damage. It is also true that just a very small part of the patient population taking ergot compounds (e.g. methysergide) do in fact develop valvulopathy. It is also worth mentioning that if a valvulopathy is detected in a patient, in all cases it disappears within a short time after stopping the medication. There is just one case documented in the literature where surgery was necessary (Graham, 1967).

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Responses to the microdosing critique reviews

David Nutt[1] and Kim PC Kuypers[2]

We would like to thank the four respondents for their thoughtful and insightful contributions to this work. We should also like to make it clear that in addition to their commentaries they also made significant observations on our critique pointing out some errors and omissions that we have taken account of to improve the manuscript. Please read the critiques with this in mind as some of their comments have now been dealt with in our text.

We were pleased that all felt it a significant contribution to the field. They also have significantly enlarged the scope of our review with their very helpful contributions to aspects such as current practice, impact on creativity, value and relevance of rodent studies to mention but a few. Where necessary we mention these issues below though much of their comments and additional insights and references reflect their extensive expertise in this field, and we are very grateful for these as they significantly improve the scientific scope and value of this critique.

A couple of their points need addressing, starting with terminology. We like the distinction made between minidose and microdose and would be happy to see this in use. A minidose being one that has a detectable effect whereas a microdose does not. Of course what the actual drug amount is for each is uncertain, and to what extent the psychoactive effect of a minidose might be 'allowed' to have and still be called 'mini' would need more consideration, but until then, Passie's suggestion of 5–15 μg LSD makes sense, though Liechti's observations need also to be taken into account.

We accept that our focus was on psilocybin and the reason for that was simple – it is almost certainly going to be the first serotonergic psychedelic made available as a medicine. For this reason, it is also currently the only psychedelic made to GMP standards and approved for medical trials with patients. This means that psilocybin is the best choice for microdosing research, certainly in patients and also for volunteer studies in countries where GMP production is required for healthy volunteers. But we fully agree that LSD should also be studied given its widespread use by the microdosing community. For those who chose to use this psychedelic then Fadiman's and Passie's approaches would make a good starting point.

The problem with all psychedelic microdosing studies is how to do it legally and ethically, and this is the big question that needs answering. Maybe a change in the regulations to exclude microdoses from the list of controlled drugs could be sought? After all, when used singly they are below the threshold for subjective effects and so are not psychoactive.

Overall, we are pleased with the results of our efforts and those of the reviewers. Microdosing is a current phenomenon whose value and safety are uncertain. Much research is needed to properly evaluate the personal psychological and health claims. We hope that this set of papers will give impetus to this research and also set it in a solid framework.

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