Microdosing with Classical Psychedelics:

Research Considerations and Practical Trajectories

Abstract

Microdosing -- the intermittent ingestion of minute, sub-hallucinogenic amounts of psychedelic substances, repeatedly and over time--has become a widespread, albeit largely understudied, phenomenon. Regulations around using psychedelics at any dose -- micro-, mini-, macro-, or mega-dose -- pose all sorts of difficulties for those who wish to systematically study the effects of Schedule I drugs, especially in the U.S. Microdosers commonly claim that taking a sub-hallucinogenic (pre-hallucinogenic or sub-perceptual) dose improves higher brain functions, including creativity, productivity, and mood. If true, these results would provide microdosing with psychedelics an important experimental edge in distinguishing psychosocial effects (e.g., caused by expectation) from those related to the active psychedelic ingredient. In this critical integrative synthesis, we explore the psychobiological science of dose amounts and how it informs microdosing with classical psychedelics (e.g., LSD and psilocybin) in order to highlight and fuel research into questions (e.g., in cognitive neuroscience, consciousness studies, and metacognition). We sketch the hurdle-laden regulatory landscape and the procedures that shroud research with Schedule I drugs. Finally, we offer some future directions relevant to both scholars and clinicians in the social and behavioral sciences as well as in mental health and neurological science.

Keywords: psychedelics, microdosing, LSD, psilocybin, placebo.

1. Introduction

The natural environment contains many psychedelic compounds; various indigenous tribes around the world have used these for thousands of years. Early evidence for such compounds appear some 3000 to 8000 years ago, long before Western culture "discovered" them in the 20th century, and before Albert Hofmann synthesized Lysergic Acid Diethylamide (LSD) in 1938 (Grinspoon & Bakalar, 1997; Pollan, 2018; Samorini, 2019). For example, native American shamans used the peyote cactus containing mescaline in their ceremonies; the Amazonian shamans used a brew of ayahuasca, containing N,N-Dimethyltryptamine (DMT), in sacramental and medicinal rituals (Andritzky, 1989); and the Mazatecs of Mexico used mushrooms containing psilocybin for similar purposes (Pollan, 2018). Taken in large enough doses, these compounds produce characteristic hallucinations, sensory distortions, mystical experiences, feelings of ego dissolution, and other symptoms of being in an altered state of consciousness (Abramson et al., 1955; Griffiths et al., 2006; Hasler et al., 2004; Liechti, 2017; Preller & Vollenweider, 2016). More recently, however, alongside a renewed interest in the beneficial effects of psychedelic substances at high doses, comes an interest in the effects of psychedelic substances in lower doses. This general, and entirely modern trend of microdosing, is currently in vogue.

1.1 What is microdosing?

Microdosing refers to the practice of consuming psychedelic substances intermittently on a systematically recurring schedule, in doses small enough to remain sub-perceptual to the user (Fadiman & Korb, 2019; Johnstad, 2018; Kuypers et al., 2019). The most common dosing schedule used is one (1) microdose every three (3) days, though schedules can vary from every other day, to weekly, or even fortnightly (Rosenbaum et al., 2020).

The most common microdose ranges from around one tenth to one twentieth of a regular therapeutic, hallucinogenic, in other words ⅒ or less of a full dose (i.e., macrodose), which are typically in the range of 100µg to 200µg of LSD (Fadiman, 2011; Fadiman & Korb, 2019; Passie, 2019; Polito & Stevenson, 2019). The microdose range for LSD -- typically between 5µg to 25µg -- has been described in informal protocols (Fadiman, 2011; Hutten et al., 2019; Polito & Stevenson, 2019), while experimental studies have used microdose ranges from 0µg (placebo) to 20µg (Bershad et al., 2019; Yanakieva et al., 2018). Some members of the research community have argued that the 15µg to 25µg range is too high a dose to warrant the designation of a "microdose;" instead, they dub such an amount as a "mini-dose" (Passie, 2019). Interviews with individuals who reported having taken up to a quarter of a full dose -- a minidose rather than a microdose -- report experiences that are not "pleasant, helpful, or generally compatible with work and everyday activities" (Johnstad, 2018). The same survey further reported "respondents sometimes found it difficult to specify the exact dose they were taking."

Microdosers of psilocybin typically ingest a median microdose of 300mg dried psilocybin-containing mushrooms, the most common method of obtaining psilocybin outside of a research context (Fadiman & Korb, 2019; Johnstad, 2018; Polito & Stevenson, 2019; Prochazkova et al., 2018). Few human experimental studies solely focused on psilocybin microdosing (aside from incidental evidence obtained from 'very low dose' arms of a larger study), compared to the number of controlled laboratory studies examining the effect of full-dose via oral synthetic psilocybin (Carhart-Harris et al., 2018; Griffiths et al., 2006; Wackermann et al., 2008). Using the rule of thumb where a microdose is 10% of a 'full-dose' (which itself is a contested quantity), the corresponding microdose for orally ingested pure psilocybin would be around 1 to 3mg. This rule of thumb seems in line with a recent, small (n=8), non-placebo-controlled study investigating the relationship between psilocybin dose, psilocin plasma concentrations, 5-HT2A receptor occupancy, and subjective drug intensity ratings (Madsen et al., 2019). One participant receiving 3mg of psilocybin experienced noticeable perceptual effects with a receptor occupancy of 43%. Thus, the authors suggest that a more appropriate microdose range for pure psilocybin would be between 0.5-2mg. Although the lack of placebo may have affected subjective intensity ratings, this study brings us one step closer to creating a more generalizable operational definition of "microdose" based on receptor occupancy or plasma concentration. In a similar vein, studies using LSD in humans to quantify maximum receptor occupancy would also be helpful in delineating the LSD microdose range.

Thus, the relative scarcity of modern studies administering carefully measured, controlled, quantities of psychedelics to participants creates a conundrum for surveys and questionnaire-like reports of microdosing. On the one hand, reported effects likely draw on a large array of actual drug doses that may be too large to meaningfully merit the diminutive appellation of "microdose" and may instead be the effects of mini-dosing (Passie, 2019). On the other hand, some users may be ingesting doses too small to be therapeutic, verging on the homeopathic. This trend becomes all the more poignant when, by operative definition, microdosing must be "sub-perceptual." So, when are benefits (or challenges) from microdosing attributable to the expectations and psychosocial circumstances surrounding the ingestion of a microdose, and how would these expectations interact with the active chemical compound? We delve into this important question later in section 2.

1.2 Why do people microdose?

Largely inspired by James Fadiman (2011), modern microdosing follows some loose protocols. This tendency has since become widely reported in the popular media, with a group of followers radiating from Silicon Valley who use microdosing to enhance productivity (i.e., as a nootropic), creativity, cognitive flow, or as a psychostimulant (Brodwin, 2017; Glatter, 2015; Hutten et al., 2019; Kotler & Wheal, 2017; Leonard & Leonard, 2015; Wong, 2017). Other groups seem more partial to microdosing as a means to generally improve mental health, boost energy, mitigate anxiety, relieve depression, reduce pain, ameliorate cluster headaches and migraines, and

enhance compassion, empathy, and spirituality (Andersson et al., 2017; Fadiman & Korb, 2019; Hutten et al., 2019; Lea, Amada, Jungaberle, Schecke, & Klein, 2020; Polito & Stevenson, 2019). Some advocates of psychedelics further sing their praises for anti-inflammatory effects based on evidence from animal models looking at the link between activation of serotonin 2A receptors and their role in the inflammatory response, and even claim potential reduction in symptoms of Alzheimer's Disease (Raz & Harris, 2016).

1.3 Why focus on LSD and psilocybin?

In this paper, our discussion focuses on microdosing with the classic serotonergic psychedelics: LSD and psilocybin. Most surveys and experimental evidence on microdosing come from either or both of these substances (Bershad et al., 2019; Johnstad, 2018; Kuypers et al., 2019; Passie, 2019; Yanakieva et al., 2018). Various online surveys on microdosing report that 48 to 68% of respondents used LSD or 1P-LSD (a chemical analogue of LSD), 28 to 58% used psilocybin, 2% used mescaline (Hutten et al., 2019; Polito & Stevenson, 2019), and between 6 to 16% used "other" psychedelics (Anderson, Petranker, Rosenbaum, et al., 2019; Polito & Stevenson, 2019). Many reasons could explain the predilection for LSD and psilocybin: for example, wider availability in more areas and the relative ease of handling compared to some of the other options (e.g., DMT, ayahuasca).

Microdosing with LSD requires hardly more than cutting up a tab or dissolving the substance in distilled water. In the case of psilocybin-containing mushrooms, using a basic scale to obtain weight-based dose or desiccating and grinding into powder allows the user to separate out smaller portions of the mushroom and overcome the problem of psilocybin being unevenly distributed across the raw mushroom. For comparison, microdosing with DMT is a more complex process because the human gut metabolizes the drug too rapidly for oral ingestion. Moreover, methods such as injecting or snorting seem impractical for repeated sessions of microdosing (The Third Wave, 2019). Lastly, DMT commonly comes in powder form. Few people have the scales and tools precise enough to dose out the small quantities necessary for microdosing. While this point also applies to LSD and psilocybin powder, the need to vaporize DMT for consumption likely decreases the consistency of the DMT microdosing experience, making it less attractive for repeat microdosing sessions. The comparatively short duration of effect also makes the use of DMT a paradoxical choice for microdosing, where the intent is to experience a protracted drug effect.

Another option for potential microdosers is to resort to ayahuasca; however, ayahuasca requires time and skill to brew as well as several agents containing monoamine oxidase inhibitors (MAOIs) to activate the otherwise digested DMT, making it harder for lay people to use practically for microdosing. Furthermore, for those already on MAOIs (e.g., for depression), taking additional unprescribed MAOIs invites potential medical complications. For those not on MAOIs, exposure to MAOIs as part of microdosing may present additional dangers and side

effects -- a deterrent to using DMT or ayahuasca for microdosing when more judicious options exist. As a case in point, ayahuasca appears in one survey wherein participants reported the three least used substances for microdosing (Hutten et al., 2019). Mescaline has also been used for microdosing; however, this psychedelic receives less attention in the literature. Thus, we focus on LSD and psilocybin in this review, as these are the drugs of choice in the context of microdosing, being more well-known and familiar than other psychedelic drugs.

We next review the existing literature on psychedelic microdosing before considering how biological and psychological factors might impact our current understanding of this research.

2. What We Already Know about Microdosing

Most of what we currently know about microdosing largely comes from informal sources such as lay people's self-experimentation and anecdotal, crowdsourced reports, collectively known as Citizen Science (Heigl et al., 2019; Irwin, 2018). But we also benefit from two (2) recent double-blind studies, one (1) open-label, naturalistic field study, and a handful of studies from the 1960s which included some form of a "low-dose" condition that could qualify as within the microdose range.

2.1 Citizen Science: Advantages and Disadvantages

Based on a collection of anecdotal reports, interviews, analysis of open, anonymous online discussion forums (e.g., reddit), and questionnaires about microdosing, we provide a summary of the reported effects from microdosing (Table 1; (Anderson, Petranker, Christopher, et al., 2019; Anderson, Petranker, Rosenbaum, et al., 2019; Fadiman & Korb, 2019; Johnstad, 2018; Lea, Amada, Jungaberle, Schecke, & Klein, 2020, 2020; Lea, Amada, Jungaberle, Schecke, Scherbaum, et al., 2020).

***** INSERT TABLE 1 ABOUT HERE *****

Table 1*: Summary of reported effects of microdosing*

Reported positive effects (↑ for "more/increased"; ↓ for "less/reduced")	**Reported negative effects** (↑ for "more/increased"; ↓ for "less/reduced")
↑energy, ↑positive mood, ↑work effectiveness, ↑health habits, ↑absorption (a measure of disposition toward intense imaginative experiences), ↑wisdom, ↑open mindedness, ↑creativity, ↑cognitive enhancement, ↑clarity of thought, ↑social benefits, ↑sensory (especially visual) sensitivity, ↑cardiovascular endurance, ↑sleep quality, ↑self-insight and mindfulness	↑neuroticism, ↑insomnia (especially if the microdose is taken late in the day) and sleep problems, ↑negative emotionality, ↑cognitive-, ↑self-, and ↑social-interference, ↑anxiety, and ↑physiological discomfort or restlessness (e.g fatigue, headaches, nausea, excessive seating, shaking, dizziness, loss of appetite, joint/muscle tightness)

↓stress, ↓migraine headaches, ↓premenstrual symptoms, ↓pain from shingles, ↓distractibility, ↓mind wandering, and ↓dysfunctional attitudes, ↓use of alcohol, cannabis, tobacco, antidepressants ↓symptoms of anxiety, depression, obsessive compulsive disorder, post-traumatic stress disorder, and narcolepsy	↓energy, ↓mood, ↓focus and concentration, ↓immune function

Aside from negative effects stemming directly from microdosing, some have reported adverse effects from consuming doses higher than a sub-perceptual microdose, resulting in unwanted psychedelic effects (e.g. visual distortions) and feelings of being too elevated or overstimulated at the end of the day (Johnstad, 2018; Lea, Amada, Jungaberle, Schecke, Scherbaum, et al., 2020). Others have also reported challenges such as: no mental health improvements from microdosing, short-lasting benefits obtained from microdosing, and feeling 'off' on days when not microdosing (Johnstad, 2018; Lea, Amada, Jungaberle, Schecke, & Klein, 2020).

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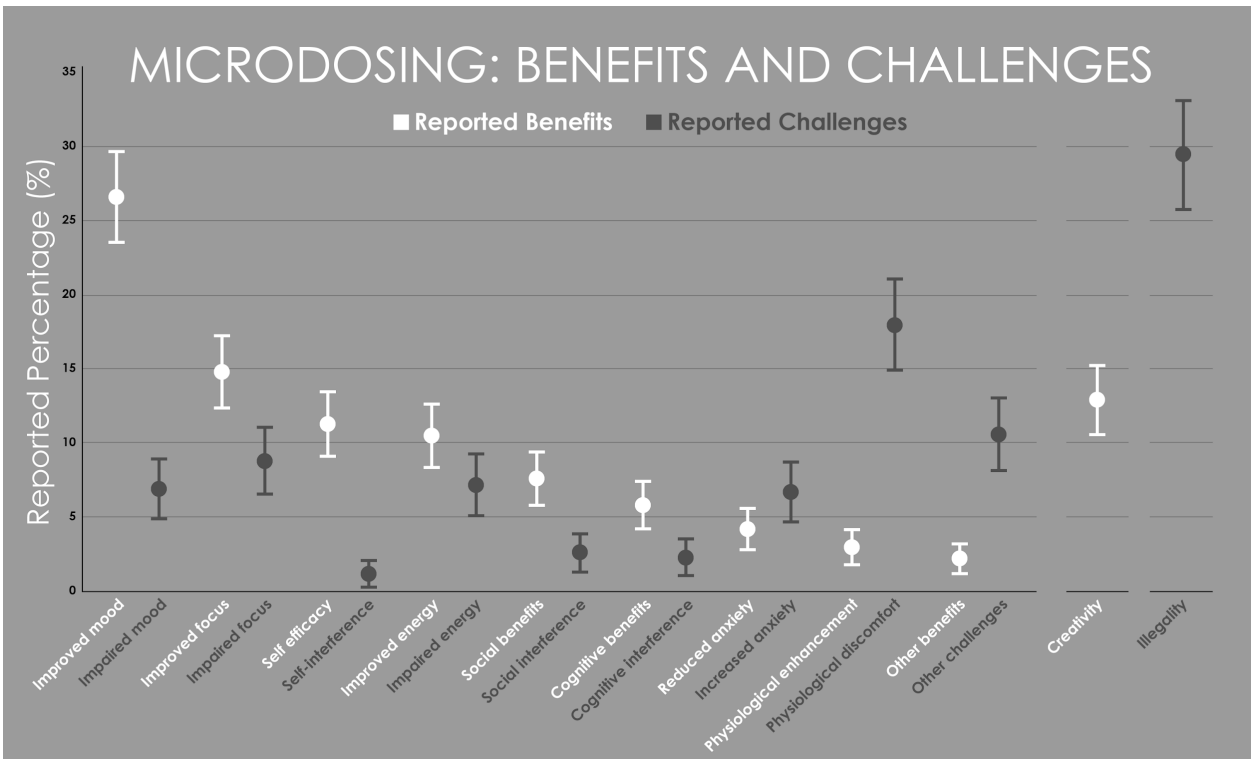

Figure 1: Self-reported benefits and challenges of microdosing. Open-ended responses from 278 respondents, who indicated microdosing with LSD-only (n=195); psilocybin-only (n=50); or

both LSD and psilocybin (n=33). (Graph created from data reported in Anderson, Petranker, Christopher, et al., 2019.)

While survey data cannot distinguish between placebo and drug effects, respondents mostly reported benefits when asked open-ended questions, whereas they reported nearly equal and opposite effects when asked specifically to describe the top benefits and top challenges experienced while microdosing (Anderson, Petranker, Christopher, et al., 2019). This pattern of response suggests that microdosing likely entails a substantial placebo component (Raz & Harris, 2016), which we expand upon in section 3.2.

Another reason for this mixed pattern of results from survey data may come from user variability in reporting microdoses and dosing schedules. Some people (ranging from 7 - 23% for 1P-LSD, LSD and psilocybin according to (Hutten et al., 2019)) do not know what dose they take because of difficulties ascertaining the purity of illegal drugs. Furthermore, it is likely that the numerical dose amounts reported by microdosers in surveys are inaccurate or imprecise estimates. One survey found that some users reported LSD microdoses as simply "$1/10^{th}$ dose" and psilocybin microdoses as "1 small shroom" (Polito & Stevenson, 2019). Another found that while most (59.6%) of their participants measured their microdoses with electronic scales, "4.5% taking psilocybin did not know dose in grams, or measured by sight (16%), with kitchen scales (1.7%), a measuring cup or spoon (1.4%) or an undisclosed method (21.3%)" (Lea, Amada, Jungaberle, Schecke, & Klein, 2020). For LSD, while it is easier to obtain more precise measurements with volumetric dosing (as about half the participants from (Lea, Amada, Jungaberle, Schecke, & Klein, 2020) reported doing), accuracy is still questionable as people can only rely on what they were told the initial dose was. Together, these comments cast doubt on whether users know the dose they are taking even if they report some number when asked to do so in a survey. Subsequently, participants likely report effects drawn from a tangle of drug substances, dosages, and schedules. Given that we are talking about microdosing, where even a few micrograms or milligrams more (or less) could result in taking too much or too little to be considered a microdose, the unknown variability of unregulated drug use drastically interferes with efforts to cull a coherent, unified pattern of drug effects from survey responses.

Beyond surveys and questionnaires, creative researchers find original ways to leverage the elements of Citizen Science with microdosing while sidestepping the regulatory burdens of dealing with quality controlled psychedelics (see section 4.1). For example, one study conducted in the Netherlands--where some truffles, but not mushrooms, are legal--collected data from microdosers who, as part of a psychedelic-themed conference they attended, consumed dried samples of truffles containing both psilocybin and psilocin (Prochazkova et al., 2018). A single, non-blinded microdose offered through this naturalistic setting (n=38) elicited improvements in convergent and divergent thinking 1.5 hours after ingestion, as measured by the Picture Concept Task (Guilford, 1967) and Alternate Uses Task (Wechsler, 2003), respectively; however, no

improvement for fluid intelligence was found, as measured with a short form of the Raven's Progressive Matrices (Bilker et al., 2012). This result seems congruent with other findings measured by the PCT in similar settings, but with macrodoses, instead of microdoses, of psilocybin-containing truffles in tea form (Mason et al., 2019). Interestingly, improvements in PCT scores only appeared seven days after participants consumed macrodoses, but not the morning after. On the other hand, some improvements in aspects of divergent thinking manifested the morning after, but not seven days later. Given this pattern of results between macro- and micro-dosing, perhaps micro- and macro-doses influence convergent thinking, as measured by the PCT, on different time scales. Whatever the explanation, and despite the methodological caveats and sample bias underlying this approach, this type of experimental resourcefulness goes a long way in paving the road to a more scientific understanding of microdosing with psychedelics.

Another novel approach blending the advantages of scale from Citizen Science while attempting to introduce more scientific rigor to the process involves attempts to recreate the double-blind aspect of randomized control trials. One microdoser created a protocol involving self-blinded microdoses of LSD. Data following self-experimentation over a period of five months showed no differences in sleep quality, memory, self-rated mood, or creativity (Branwen, 2012, https://www.gwern.net/LSD-microdosing). On a similar but larger scale Szigeti et al. (2021) used an innovative and intricate protocol to conduct a within-subjects, self-blinding microdosing naturalistic study with one of the largest sample sizes in the literature (n=191). Using non-human readable QR codes, non-transparent capsules to create psychedelic and placebo microdoses, and shuffled envelopes to randomize the now-blinded microdoses, investigators created a method for participants to microdose themselves while being blinded to the substance they were microdosing with. This entire process was conducted at home during a core microdosing period of 4 weeks. The investigators were able to later recover information revealing what substance was within each capsule by scanning the machine readable QR codes associated with each microdose. This type of effort allows for larger samples, richer data, and additional ways to further elucidate the effects of microdosing, while requiring the usual caveats: We cannot be confident how closely each participant follows the self-blinding protocol in letter or in spirit (both or neither), what other things they may be doing, what drug quality and dose they use (and how trustworthy their reporting), and what (hidden) agendas they may wish to promote. However, even with such overarching drawbacks, these anthropological-like assays can inform and shed empirical light on the growing culture of microdosing. Thus, although Citizen Science comes with multiple caveats, it may -- as noted by James Fadiman -- "provide a useful tool for doing a massively parallel 'search'" to draw the outer bounds of the hypothesis space without regard to false positives. However, the bridge separating fact from fad should be built on solid scientific research.

2.2 Beyond Citizen Science

A small, double-blind, placebo controlled, randomized controlled trial with repeated microdoses in older healthy adults (55-75 years) provides insight into the boundaries between microdose and minidose (Yanakieva et al., 2018). Thirty-six participants ingested 5µg, 10µg, or 20µg of LSD (n=12 per dose level) six times, once every three days. The study reports some slight distortions in time perception at the 10µg dose level. However, no statistically significant effect of LSD at any dose-level was found for self-reported measures of perceptual distortions, unusual thoughts, concentration, feeling high, or feeling a drug effect, when measured every half hour, through seven hours post-microdose. This result stands in contrast to another recent double-blind study with younger (19-30 years), healthy participants, who received single microdoses of LSD at 4 different dose levels of 0µg (placebo), 6.5µg, 13µg or 26µg (Bershad et al., 2019). This latter study reports increased ratings of feeling a drug effect with both the 13µg and 26µg dose, but affirms that 6.5µg does little to produce any difference in ratings. At 26µg, participants reported an increase in "feeling high." Taken together, these studies suggest that the threshold between a "sub-perceptual" microdose and a minidose lies somewhere between 20µg and 26µg.

Improvements in mood, creativity, and cognition serve as some of the most cited motivations for microdosing (Hutten et al., 2019; Polito & Stevenson, 2019). However, results from studies involving a single microdose of LSD did not show significant effects on convergent thinking when measured by a remote associations task (Bershad et al., 2019; Mednick, 1968), whereas naturalistic Citizen Science survey reports mixed results. Non-blinded naturalistic studies and surveys tend to find increases (Anderson, Petranker, Rosenbaum, et al., 2019; Prochazkova et al., 2018), while studies accounting for participant blinding do not (Szigeti et al., 2021). Evidence is starting to accumulate suggesting that the effects of microdosing–while real and potentially clinically significant–may not exceed placebo effects. Thus, studies controlling for the quantity and quality of substance consumed are sorely needed in this area to provide higher quality evidence on this hypothesis.

Moreover, 2.5 hours after ingestion of LSD, mood and cognition (i.e. working memory) did not change (Bershad et al., 2019). However, it is important to keep in mind that the experimental studies have smaller sample sizes, and thus statistical power, than naturalistic survey reports. Other reasons may explain the differences between the experimental studies and survey reports could be: blinding and expectancy effects, biased samples, substances used (synthetic LSD vs. truffles containing psilocybin and other elements), specific measure of convergent thinking used (i.e., the PCT appears to be especially sensitive), study design, time of measurement, number of microdoses taken, as well as additional factors. Formal experimentation with microdosing is still in a very preliminary stage, and will need many more instances to substantiate null effects. All of these seemingly contradictory results should be clarified with further research.

In addition to effects on creativity, mood cognition, microdosing affords a unique opportunity to probe other fundamental questions on consciousness, brain plasticity, and belief formation. Because of the wide variety of motives and beliefs microdosers hold towards microdosing with psychedelics, there are a multitude of interesting exploratory research avenues one could pursue, such as characterizing the effects, if any exist, on sleep architecture (e.g., to look into reports of insomnia from Citizen Science); measures of functional brain complexity as another possible index of creativity (e.g., the Perturbational Complexity Index (Casali et al., 2013; Casarotto et al., 2016; Gallimore, 2015)) and effects on social and group dynamics to explore claims of increased empathy, cordiality, and other social benefits.

3. What's in a (micro)dose? Placebo effects and contextual factors in determining a 'dose' as applied to microdosing

The term microdosing is easy to misconstrue. The juxtaposition of the two words--"micro," extremely small or 10^{-6}, and "dose," a measured amount of substance -- requires a bit of clarification. Stemming from the drug development process, the general term "microdose" typically refers to 1% of the pharmacologically active dose, up to 100µg, regardless of the drug (Kuypers et al., 2019). However, when it comes to microdosing with psychedelics, little formal scientific consensus prevails regarding how small (or large) a dose should be to live up to the label "microdose." (Kuypers et al., 2019; Lea, Amada, Jungaberle, Schecke, Scherbaum, et al., 2020; Passie, 2019). Passie (2019) suggests that 20 µg for LSD is considered by many to be the threshold for a microdose, but also mentions that there are two different definitions of microdosing in the literature: one that involves no detectable acute effects, and one that involves "some detectable effects" but yet allows for enough control to fully function in normal circumstances (Austin 2018, cited in Passie 2019). As mentioned in the previous section, (Bershad et al., 2019) provide evidence that some people experience detectable subjective effects already at 13 µg for LSD.

Furthermore, deriving a 'microdose' as a proportion or percentage of a regular, full-dose, is not scientifically useful, because a recreational dose is itself not well specified. Depending on the user, a recreational dose could be anywhere between 50 µg – 250 µg (Nichols & Grob, 2018; Passie, 2019; Polito & Stevenson, 2019), though the most common use refers to 100-200 µg for LSD (Haden & Woods, 2020; Lea, Amada, & Jungaberle, 2020). Pragmatically, everyday users who obtain LSD through unregulated channels can only use measures such as "1 tab" to represent a standard dose (Lea, Amada, & Jungaberle, 2020). However, there is no guarantee of the concentration or quality of drug in a tab obtained by such channels, so concentrations could (and likely do) vary between sellers and between batches. For psilocybin, practical measures such as "1 small mushroom" of dry or fresh weight (Lea, Amada, Jungaberle, Schecke, & Klein, 2020; Polito & Stevenson, 2019) can have individual and species-specific variation in

concentration and proportion of psilocybin, psilocin and other potentially unidentified psychoactive ingredients (Kuypers et al., 2019). The commonly mentioned 5% - 10% of a 'regular' dose may work as a social, preliminary, and pragmatic, consensus but is not necessarily a scientific consensus.

Thoroughly pinning down the acceptable range of a microdosing is important, as in some drugs, it is a change in the dose, rather than the substance that targets different brain receptors and serves different therapeutic purposes (Stahl, 2013). For example, in low doses, psychiatrists may prescribe trazodone as a hypnotic (inducing sleep) agent, but in higher doses, trazodone may be prescribed as an antidepressant (Stahl, 2013). This clinical phenomenon comes about as a function of the pharmacodynamics and psychobiological factors associated with the way chemicals affect physiology and behavior (Kaypak & Raz, n.d.)this issue).

We next elaborate on when substrates are, or are not, biologically, psychologically, and therapeutic equivalent. These factors serve key roles in any use of a drug, but are especially crucial to consider in the context of microdosing with classical psychedelics, which we argue are especially susceptible to placebo effects. Our discussion touches on how the science of dose variation can guide and shape the future of dosing--including microdosing -- with psychedelic drugs, which possess a rather wide therapeutic index (i.e., good safety) -- within a framework of narrow therapeutic index and critical dose drugs, including a few lessons gleaned from clinical cases.

3.1 Biological Equivalence

Even before considering psychedelics, their effects, and how they compare to each other, the concept of biological equivalence requires clarification. For example, in principle, generic medications are biologically equivalent (bioequivalent) to their brand-name counterparts; they offer the same therapeutic effect at a reduced cost. However, generics can differ from their name counterparts even for the active ingredients. Generics can be plus-or-minus a certain percentage off from the formula or recipe of a name drug. For most drugs, these small variations would make little, if any, difference, but on some occasions and for certain individuals, the biologically disparity between name and generic drugs may actually entail a big change.

For example, just before 2000, a generic version of Diclofenac -- a nonsteroidal anti-inflammatory drug (NSAID) used to treat mild to moderate pain, fever, and inflammation -- correlated with unexplained melting of the cornea (Mian et al., 2006). More than a decade later, around 2012, accounts again surfaced reporting a similar trend with generic NSAIDs. It turned out the drug switch -- from name to generic--seemed to be the root cause for the problem. Assuring the patient that the branded NSAID and the generic were exactly the same (i.e., by pointing to Ketorolac as the active ingredient), could lead to a drug choice that would potentially result in a corneal melt.

Again, we recall that the active ingredient is just one part of the drug. Unlike with systemic medications, it appears that other components that make the drug (e.g., excipients) can have a dramatic impact on the human eye. The fear of corneal melts is having a real impact in eye doctors' offices: some ophthalmologists even require patients to sign a written consent detailing the advantages and disadvantages of the branded versus the generic NSAIDs due to the high risk of developing cystoid macular edema, a now-identified complication of generic NSAIDs.

Bioequivalence becomes especially relevant in the psychedelic arena, where Citizen Science surveys show that people microdose with different chemical derivatives of classical psychedelics (Hutten et al., 2019; Polito & Stevenson, 2019). For example, microdosers report using 1P-LSD, LSZ, and 1A-LSD/ALD-52 -- different analogs of traditional LSD (LSD-25) -- under the tacit assumption that all these variations form bioequivalently functional comparables with LSD. However, science is yet to establish their comparability.

Similar to variations of LSD, the composition and quantity of active psychedelic material in any given mushroom, even within the same species, follows natural variation (e.g., due to time of harvest, preservation conditions, growth environment), even within the same species. In addition, psilocybin-laden mushrooms do not contain psilocybin only; they also carry other potentially psychoactive compounds such as baeocystin, norbaeocystin, and the active metabolite of psilocybin, psilocin (Gotvaldová et al., 2021; Kuypers et al., 2019; Prochazkova et al., 2018; Sherwood et al., 2020). Thus, dose and experience likely vary as a function of species (Kuypers et al., 2019). Whereas in Citizen Science "almost anything goes," in science we mostly draw on precise measurements of the pure form of synthetic psilocybin. The difference between these two disparate approaches makes for a difficult comparison.

Taking one step further, not only are analogs of LSD and different species of psilocybin-containing questionably biologically equivalent within their own category, LSD and psilocybin are sometimes also treated as biologically equivalent or interchangeable with each other in most informal contexts. Informal guidelines exist suggesting dosage equivalencies between LSD and psilocybin (*Microdosing Dosage and Regime*, n.d.; *R/Microdosing - Dose Discussion*, n.d.). Such parity relies on the phenomenological "feel" of the experience when taking one or the other drug. While, research dating back to the 1950s suggests that it may be possible to quantify comparative macrodoses in terms of effects on physiology and cross-tolerance (Isbell, 1959; Isbell et al., 1961; Wolbach et al., 1962), the criteria for comparisons remains unstudied, despite, anecdotally, centering around the quality and degree of hallucinations. One survey found that psilocybin-only microdosers rate the importance of microdosing benefits higher than LSD-only microdosers, but there were no differences to those who microdosed with both LSD and psilocybin, and no differences were found for microdosing challenges (Anderson, Petranker, Christopher, et al., 2019). Another finds no differences between LSD and psilocybin on mental health vulnerability, wisdom, negative emotionality, open-mindedness as measured by questionnaires (Anderson, Petranker, Rosenbaum, et al., 2019). One caveat to consider when

evaluating these studies involves culture-specific differences in substance availability. Local availability of LSD, psilocybin mushrooms, peyote cacti, etc. may systematically differ by region, and thus, results on reported effects of microdosing by substance may be confounded with culture. So while these surveys are a good start into investigating the comparative effects of substance specific microdosing, there remains a large gap in our understanding of substance specific effects in the microdosing literature.

The practices associated with the storage and consumption of psychedelic microdoses form another consideration relating to biological equivalence. With LSD, for example, comments on Reddit--one of the most-popular sites in the United States (and worldwide) featuring a massive collection of forums, where people can share news and content or comment on posts--recommend dissolving LSD-containing blotters in distilled water or alcohol, and caution against mixing with tap water or exposure to sunlight, under the assumption that doing so would slow down or prevent the degradation of LSD (Li et al., 1998; The Third Wave, 2018). One survey shows that amongst those surveyed who microdosed with LSD, roughly the same percentage of people dilute LSD with alcohol (commonly vodka) as with water, whereas 9.5% reported dilution with other liquids (Lea, Amada, Jungaberle, Schecke, Scherbaum, et al., 2020). However, due to variability in how people consume microdoses, it is unclear whether the purported effects of microdosing may be partially due to consumption of the excipient alcohol or to the other filler substances combined in the microdoses. In contrast, outside of research, consuming psilocybin-containing mushrooms follows three different forms: raw, desiccated, or imbibed in tea form. This variation in microdose preparation may well lead to a lack of bioequivalence across users, and therefore across reported effects. The field is still in its infancy, and basic questions—e.g., whether using water or alcohol as the solvent makes a difference to the effects of microdosing, or whether interaction effects between dose and excipient occur—remain currently unanswerable with surveys or typical citizen science methods.

3.2 Psychological Equivalence and Placebo Effects

Bioequivalence hardly implies psychoequivalence. To illustrate the importance of psychological equivalence, consider the labelling of brand-name and generic-drugs again. Perception of brand versus generic medications can meaningfully impact reported and measured effects, including tolerance to specific medication. For example, when undergraduate students who reported suffering from frequent headaches ingested brand-name ibuprofen, generic ibuprofen, or placebos labeled as either brand-name or generic, those who ingested brand-name placebos reported fewer side effects than those taking generic-labeled placebos—perhaps because the students thought that the branded medications would introduce a treatment benefit (Faasse et al., 2016). In another study, students received placebos, which they thought were beta-blockers, to treat exam-anxiety. All participants started with a brand-name placebo (“Betaprol”), followed by measurements of blood pressure and anxiety levels. Thereafter, a random procedure instructed some participants to continue with the brand-name placebo, switch to a different brand-name

placebo ("Novaprol"), or receive a generic-labeled placebo (Faasse et al., 2013). The group that continued taking the brand-name placebo showed statistically significant decreases in blood pressure and anxiety relative to either the group that switched to the alternate brand name or to the generic-labeled placebo. Even more telling, the latter two groups also reported heightened side effects, compared to Betaprol users. Thus, psychosocial factors, not just chemistry, can influence drug effects.

Recalling the mixed pattern of microdosing reports summarized in section 2.1, the strong motivations and expectations surrounding psychedelic microdosing, and the ambiguity involved in taking a "sub-perceptual" or "sub-hallucinogenic" dose where it is difficult for the microdoser to verify what they have taken, it is likely that microdosers will be susceptible to placebo effects. One recent study has shown that it is possible to induce a psychedelic-like experience in some people given placebos when placed in an appropriate context that created high expectations of being given a full-dose psychedelic (Olson et al., 2020). Given the more subtle experience of microdosing, it may be that psychedelic microdosing operates on similar principles. Perhaps in specifically asking questions aimed at eliciting reports of benefits or challenges related to psychedelic microdosing, the question frames the expectations of the user responding, hence providing the interesting pattern of equal and opposite effects we saw in section 3.1.

Additionally, we may already have one such example of placebo effects operating on psychedelic microdosers in the naturalistic study by (Prochazkova et al., 2018). The participants were part of a psychedelic-themed conference and agreed to participate in the study, and thus likely already positively inclined towards psychedelics. The study was non-blinded, and open label placebo studies have already shown that placebo effects occur even in the absence of deception, and can ameliorate symptoms of irritable bowel syndrome and chronic lower back pain (Carvalho et al., 2015; Kaptchuk et al., 2010). The study found improvements in creativity but not fluid intelligence. Because studies have found that placebos can enhance both creativity and fluid intelligence, we might expect improvements to both in (Prochazkova et al., 2018). However, we also know more people are motivated to microdose to enhance creativity, whereas fewer than one in five do so with cognitive enhancement as their primary motivation (Foroughi et al., 2016; Lea, Amada, Jungaberle, Schecke, & Klein, 2020; Rozenkrantz et al., 2017). Recent evidence from Szigeti et al. (2021), which found the level of participant blinding was a significant predictor of mood improvement from microdosing, further lend support to the hypothesis that the difference in microdosing motivation may explain the difference in microdosing effect.

Furthermore, varying perceptions of illegality about the choice of drug used in microdosing may contribute to differing expressions of placebo effects. Microdosers who opt to use analogs of LSD may be doing so due to ease of access or perhaps because they harbor the sentiment that these chemical formulations are less illegal than the Schedule 1 LSD (i.e., because the analogs are not explicitly on the schedule). Although true in some countries (e.g., in Canada, 4-AcO-

DMT is not illegal whereas psilocybin is, both are metabolized into psilocin), in the USA, using analogs could still lead to prosecution. The 1986 Federal Analogue Act deems any chemical--intended for human consumption and "substantially similar" to a controlled substance listed in Schedule I--as if it were listed in the schedule. And yet, the "optics" (i.e., of using some substances that appear less illicit), albeit legally specious, may render these analogs psychologically "un-equivalent" to the original.

3.3 Therapeutic Equivalence

Psychedelics differ from one another not only in their active ingredients, purity, excipients, etc. but also in their method of delivery, rendering substances that are otherwise chemically identical nevertheless therapeutically dissimilar. Let us consider a non-psychedelic example to illustrate the psychedelic situation. EpiPens—spring-loaded syringes filled with epinephrine—keep airways open during severe allergic reactions, especially in children. These devices are expensive largely due to lack of competition and generic alternatives. Some individuals and families resort to creating make-shift injections by buying regular syringes from a local pharmacy and epinephrine ampules to fill them with. However, unlike EpiPens which last a year, these would expire within three months and are more complicated to get the correct dose and administer it safely with such an improvised syringe.

With this backdrop, an American pharmacy chain (CVS) tried to change this situation by introducing a generic version, Adrenaclick. However, because the injecting mechanism used by Adrenaclick differs from that used by EpiPens, the FDA decided that the two products are not *therapeutically equivalent* due to insufficient evidence of their equivalency. When two products are not therapeutically equivalent, a prescription for one cannot be filled with the other. Thus, consumers would need to know the distinction, which prescription would get them the less expensive generic alternative, or perhaps the more effective option.

Differences in delivery systems could render two otherwise similar drugs therapeutically un-equivalent. In microdosing, this point takes on special importance, especially if, in the future, psychedelic microdosing becomes a viable target of regulatory approval. While most microdosers ingest orally, a spectrum of intake options (e.g., sublingual, inhaled, intranasal, and rectal) may affect outcome (Kuypers et al., 2019). Specifically, two recent double-blind studies administered LSD sublingually and orally, respectively (Bershad et al., 2019; Yanakieva et al., 2018). Formally, we cannot consider results from these two studies as coming from a therapeutically equivalent form of LSD microdosing. Given the case of ketamine discussed in the section below, we also believe that differences in administrative routes could affect drug effectiveness. This is important to consider especially in the context of microdosing because this could lead to different clinical recommendations should psychedelic microdosing become approved as a treatment in the future.

The insights and sensibilities of seasoned clinicians contribute greatly to our understanding of the therapeutic potential of psychedelics (e.g., see Kaypak & Raz, this issue). Given that a common motivation for microdosing is some form of self-managed therapy, either alone or in conjunction with other treatments (Lea, Amada, Jungaberle, Schecke, & Klein, 2020; Lea, Amada, Jungaberle, Schecke, Scherbaum, et al., 2020), a discussion of both psychedelic and non-psychedelic factors affecting clinical outcomes is valuable in assessing microdosing's potential therapeutic contribution.

For example, ketamine is a dissociative drug made from a 1:1 mixture of esketamine and R-ketamine molecules. It produces hallucinogenic effects and is a commonly prescribed on-label as an anesthetic, but has been used off-label by clinicians as an effective treatment for treatment-resistant depression. Ketamine clinics administering ketamine for depression do so via IV, and most studies demonstrating potent antidepressant effects are conducted using this route of administration (Han et al., 2016; Sanacora et al., 2017; Singh et al., 2016; Wilkinson et al., 2018). However, by the time ketamine made it through the FDA approval process, the approval was only for esketamine (Spravato) administered through nasal spray (Commissioner, 2020). Putting aside the molecular differences chosen for patentability, the nasal route of administration was chosen to balance a fast-acting route of administration with the relative convenience of patients self-administering the drug (Paddock, 2019). From the original observation of strong anti-depressant effect to FDA approval, the molecule and route of administration has changed enough to make one question if the approved esketamine might differ in efficacy from IV ketamine. The efficacy of nasal esketamine compared to IV ketamine has yet to be determined, though preclinical studies suggest esketamine may be less effective than ketamine and that nasal administration is ineffective due to the difficulty of properly self-administering the drug (Gálvez et al., 2018; Zhang et al., 2014).

Currently, most of the drugs illegally obtained for microdosing are only available at unverified concentrations, with set excipients, and via specific delivery systems. Moreover, this variation changes depending on drug dealers and geographical location. While some surveys of microdosers ask participants about the drug and dose they use, there is little mention of how, if ever, participants substantiate their answers (Hutten et al., 2019; Lea, Amada, Jungaberle, Schecke, & Klein, 2020; Polito & Stevenson, 2019). To consume a microdose of the same substance obtained in New York City, Montreal, or Los Angeles likely involves vastly different chemical experiences at multiple levels of potential equivalence. Moreover, the ketamine example above illustrates how drugs intended for clinical purposes - which may be equivalent biologically, pharmacologically, psychologically, in concentration, excipients, or route of administration - may be transformed along the approval process so that by the time a patient obtains the prescription, its efficacy may be far removed from the potency of the original, evidence-based benefit. Given that many people are explicitly motivated to microdose for therapeutic benefits (Johnstad, 2018; Lea, Amada, Jungaberle, Schecke, & Klein, 2020; Lea, Amada, Jungaberle, Schecke, Scherbaum, et al., 2020), this discrepancy suggests caution in

translating benefits obtained in controlled laboratory environments to the real world so that unforeseen factors do not interfere with any established clinical benefit. It may therefore be wise to explore a variety of delivery systems in order to provide recommendations on the best delivery system that maximizes clinical and therapeutic outcomes.

3.4 Narrow Therapeutic Index and Critical Dose Drugs

Narrow Therapeutic Index (NTI) drugs refer to medications that possess a narrow margin between the amount that is safe-and-effective and the amount that is dangerous-and-toxic. Technically, this margin is defined as less than a two-fold difference in median lethal dose (LD50) and median effective dose (ED50), or less than two-fold difference in the minimum toxic concentration and minimum effective concentration in the blood.

NTI drugs sometimes bleed into the appellation of "critical dose drugs." The definition of such drugs stipulates that comparatively small differences in dose or concentration may lead to dose- and concentration-dependent, serious therapeutic failures and/or serious adverse drug reactions. Such deleterious results may be persistent, irreversible, slowly reversible, or life-threatening events. Possible examples of such drugs include phenytoin (anti-seizure medication for epilepsy), digoxin (for heart conditions), cyclosporine, warfarin, theophylline, lithium, and levothyroxine. With these drugs, if the dose is even marginally off, one could experience noticeable symptoms of over-treatment (too much medicine) or under-treatment (too little medicine).

To be clear, classical psychedelics seem relatively safe and do not, nor have ever, presented a lethal risk from the ingestion of the compounds themselves (*Microdosing Dosage and Regime*, n.d.; *R/Microdosing - Dose Discussion*, n.d.). Indeed, a group consisting of experts in addiction, chemistry, pharmacology, forensic science, psychiatry and other medical specialties, including epidemiology, as well as the legal and police services have rated LSD as less harmful than commonly available drugs such as alcohol, tobacco, buprenorphine and cannabis (Nutt et al., 2007). Based on interviews, the main challenge with microdosing seems to include the consequences of accidentally taking a dose beyond a microdose (i.e., verging on a mini-dose), and insomnia (Johnstad, 2018). These preliminary reports suggest that the largest behavioral problem seems to lie in accurately consuming a microdose instead of more, which in the case of LSD, for example, amounts to a few micrograms (Johnstad, 2018). We are arguing that dose sensitivity (illustrated by NTI drugs), but crucially, not lethality, is an especially important consideration in psychedelic (micro)dosing, where a sharp change in effect can be brought about by a small change in dose, just like NTI drugs.

Psychedelic microdosing may lead to NTI-like behavior, with the important exception that the consequences of overdosing are typically far less dangerous than death, or permanent, irreversible, life-threatening damage associated with many NTI drugs. However, the threshold between microdosing and minidosing still traverses a boundary with real health consequences.

Furthermore, as microdosing, by design, involves repeated ingestion of psychedelics over a period of time, research into the long-term effects of psychedelic use must assess the safety of this practice. Kuypers et al. (2019) for example, highlight the possibility of cardiovascular risks associated with the activation of serotonin 2B receptors, though preclinical studies in animal models have not revealed any such risks. Clarifying the parameters of that boundary is not only theoretically and scientifically useful but also pragmatically significant for the many who engage in microdosing with psychedelics.

3.5 What's in a (Micro)Dose? Summary

For most users, microdosing with psychedelics entails the "use of a low dose below the perceptual threshold that does not impair 'normal' functioning of an individual" (Kuypers et al., 2019), but contains within it a fringe paradox: on the one hand, individuals take operationally sub-perceptual doses; on the other hand, they expect some--presumably perceivable--benefit. This apparent incongruence may come from using the term "sub-perceptual" in the context of microdosing than anything else. What is the perceptual threshold? Whereas clinicians usually define sub-threshold as sub-hallucinogenic -- in other words, any dose that does not produce marked alterations in perception -- in cognitive science, sub-threshold usually means subliminal, or below the threshold of conscious awareness. In this latter sense researchers use "sub-perceptual" for describing presentations (e.g., visual, auditory, tactile) that affect behavior but are largely unavailable to the conscious experience of the participant. Thus, unrelated to subjectivity, practitioners and researchers may entertain two different operational interpretations in defining a microdose. Plus, amongst the general population, what individuals mean when they refer to "sub-perceptual" likely falls in different spots along this hazy range.

Exacerbating the problem of what it means to take a "sub-perceptual" microdose, microdosing as currently practised, is hardly biologically, psychologically or therapeutically equivalent between any two users.

The term "bioequivalent" turns out to be tenuous: there is a lack of consensus not just between practitioners and scientists, but also among pharmacists (e.g., (Kirking et al., 2001; Vasquez & Min, 1999), physicians (Berg et al., 2008; Reiffel & Kowey, 2000), and consumers (e.g., (The Epilepsy Foundation, 2006). It seems that, at least in certain clinical contexts (e.g., specialized eye surgery and treatment), taking brand or generic versions of drugs has been shown to make a difference. Perhaps the same could apply to different analogs for LSD, or different mushroom species for psilocybin.

Placebo studies illustrate how psychological factors might amplify (or diminish) drug effects. In the context of "sub-perceptual" microdosing, it is especially interesting to consider how, why or which psychological factors might lead some microdosers to attribute effects (e.g., on mood, creativity, focus etc.) to the psychedelic drug used.

At least for some critical dose drugs, one should exercise special caution because even bioequivalent drugs may be dissimilar in their effects on therapeutic goals and various clinical parameters. This variation forms a nuanced and complex intake dynamic. Minute variations in active drug ingredients, including different excipients and routes of administration, can add up to entail tremendous changes for the end user.

Now that we have clarified biological equivalence, psychological equivalence, therapeutic equivalence, narrow therapeutic index, critical dose drugs as they relate to the research content on microdosing with psychedelics, we turn to a practical sketch of navigating the regulatory requirements for conducting research on psychedelic microdosing in the USA, in hopes of encouraging an increase in microdosing studies beyond Citizen Science.

4. Research with LSD and Psilocybin: Navigating Regulation

In the U.S., in order to conduct research with LSD, psilocybin, or any other Schedule I controlled substance, researchers must obtain approval from the FDA via an application for an Investigational New Drug (IND). In addition to the FDA's granting permission to administer drugs to participants, the Drug Enforcement Administration (DEA) must issue a license permitting the storage and distribution of the drug at a research facility. Also, as they would with any experiment, researchers must also receive approval from an Institutional Review Board (IRB) to maintain ethical research standards and protect the privileges of participants. Moreover, in some states (e.g., California), researchers may need to obtain additional authorization from a local research advisory group (e.g., Research Advisory Panel of California or RAPC). While the DEA requires approvals from the FDA and IRB before processing an application for a license, RAPC-like committees usually accept proposals even with IRB approval still pending.

The FDA requires detailed information related to three different domains: 1. Research protocol and experimental design; 2. Chemistry, manufacturing, and control of the substance required for the protocol; and 3. Pharmacology and toxicology data regarding the substance (available on the websites of the Multidisciplinary Association for Psychedelic Studies (MAPS) and the Usona Institute, where Investigator's Brochures with detailed accounts of the pharmacology and toxicology of psilocybin and LSD are also downloadable (Jerome, 2019; Usona Institute, 2018)).

A multitude of studies, conducted between the 1950s and 1970s, have examined the safety of LSD in humans (Abramson et al., 1955; Isbell, 1959; Jarvik et al., 1955; Levine et al., 1955; Passie, 2019). LSD is hardly a new drug; as such, requiring INDs to conduct non-clinical research with LSD--usually reserved for new drugs untested in humans entering phase I or phase II of clinical trials--to demonstrate safety, efficacy, and tolerability, may seem unnecessary. However, likely because of historical, cultural, and countercultural use in the 1960s (Hartogsohn,

2020), the specific connotation LSD still holds within the U.S. means that human studies using LSD within North America have rarely been conducted without an IND.

4.1 Obtaining Psychedelics for Research

Whereas researchers embedded in a large academic medical school environment may obtain psychedelic drugs in-house through a local pharmacology department (e.g., University of Wisconsin, Madison), most scholars face a challenge in obtaining research-grade psychedelic substances. For research proposes, scientists must work with drugs that are high in purity, and quality controlled; getting drugs from dealers on the street, who promise their product is "pure" and "the best quality," may work for Citizen Science but hardly for formal research. To ascertain drug safety, the FDA may require that researchers use suppliers who adhere to current Good Manufacturing Practice (cGMP) regulations, or at least suppliers who can provide detailed spectral and analytical data on the drug to be used (Center for Drug Evaluation and Research, 2019). cGMP dictates that the methods, facilities, and controls used in the manufacturing, processing, and packaging of a drug must be consistently well-documented, traceable, and replicable. The cGMP protocol ensures that manufacturing claims regarding quality and quantity of a drug maintain a minimum standard of safety and consistency. However, only few manufacturers and suppliers produce psychedelic drugs to such a standard (see Table 1). While non-clinical research does not formally require cGMP-grade drugs, in coming to evaluate research proposals involving the ingestion of psychedelics by human participants, both the FDA and IRB would likely insist on this standard. Moreover, the FDA expects this standard from all IND applications submitted for phase II and phase III studies.

***** INSERT TABLE 2 ABOUT HERE *****

Table 2: *Only a handful of commercial, or non-profit, manufacturers provide research-grade (cGMP) psilocybin; fewer still produce cGMP LSD. Geared towards clinical trials and therapeutic agendas, obtaining psychedelics from some of these sources may require signing non-disclosure agreements;* (Goldhill, 2018). *At least in one case, researchers were employees of the company that provided the LSD* (Yanakieva et al., 2018).

Company Name	Type of Organization	Psychedelic Produced or Primarily Used	Profitability	Area of Operation	Related Studies	Other Notes
Organix Inc.	Contract chemical manufacturer	LSD, Psilocybin, Psilocin	Private, for profit	Massachusetts, USA	Provided LSD to Bershad et al. (2019)	DEA licensed for substances on Schedules I-IV and their derivatives or analogs.
Eleusis Benefit Corp (USA) / Eleusis Pharma-ceuticals Ltd. (U.K)	Commercial research	LSD	Private, for profit	London, U.K, New York, USA	Eleusis Benefit Corp (USA) funded Yanakieva et al., (2018)	
COMPASS Pathways	Commercial research	Psilocybin	For profit	Europe, North America	Clinical trials forthcoming	Achieved "breakthrough therapy designation" for psilocybin from FDA. May provide our cGMP psilocybin to researchers free of charge, in exchange for the right to use safety data. Researchers are expected to cover packaging and shipping costs with our logistics provider.
Usona Institute	Research organization	Psilocybin	Non-profit	USA (2 DEA licensed chemical laboratories in Madison, WI, and San Luis Obispo, CA)	Clinical trials forth coming	Usona will provide psilocybin to qualified researchers at no cost. Anyone who makes a request to receive psilocybin for research purposes must submit full protocol and other documentation for review and evaluation.
Onyx Scientific Ltd UK	Contract chemical manufacturer	LSD, Psilocybin	For profit	Labs in U.K and India,	Provided LSD to Yanakieva et al., (2018) Funded by Eleusis	Exclusive manufacturing contract with COMPASS pathways for cGMP psilocybin.

Whereas obtaining cGMP psychedelics at the macrodose level poses a moderate challenge, acquiring microdoses is more complicated because companies usually produce cGMP psychedelics at pre-set macrodose levels. Fabricating microdoses increases production costs and creates other hurdles required to accurately and precisely create such low doses. Without professional finesse, special facilities, and pharmaceutical skills to create consistent microdoses, a tiny variation within a few micrograms may constitute the difference between a microdose and a minidose. Unfortunately, taking a typical macrodose -- say, a 125µg cGMP LSD pill--only to further subdivide it into ten (or twenty) microdoses at the research site is difficult. Not only would additional permits, physical infrastructure, and logistical overhead be required, doing so would typically nullify cGMP standards. This pertinent consideration becomes all the more relevant when conducting research outside of research universities or medical schools, which benefit from in-house resources to receive, handle, store, and re-package psychedelic drugs into a ready-to-use product. Bureaucracy aside, costwise, for cGMP psilocybin, researchers would pay $7,000-10,000 per gram while in the streets, lay people could obtain one gram of magic mushroom for about $10. However, this discrepancy (two orders of magnitude) reflects not just the differences between pure synthetic psilocybin and "shrooms" obtained on the street, but encapsulates the manufacturing process, systematic study, and accountability to which scientific research aspires to and mandates.

Finally, the delivery system of microdoses not only plays a role in the logistics, but also in the methodology of such experiments. Intravenous procedures may provide accurate dosing, but they are invasive and require the participation of a clinician or phlebotomist. However, capsules ingested orally seem more congruent with experimental designs intended to tease apart the effects of participant selection and free will (Raz & Zigman, 2009). For example, providing capsules to participants who then themselves choose the number of capsules they ingest could pave the road for studies looking at the interactions between self-efficacy, locus of control, and psychedelic microdosing (Bandura, 1982; Judge et al., 2002).

Some scholars may carry out their research in institutions whose IRB may possess neither experience nor expertise dealing with psychedelics. In such cases, researchers should contact an external, commercial IRB (e.g., Western IRB). Although external IRBs receive payment for their services and may foster the optics of a conflict of interest (e.g., you appear to "buy off" their protection of the rights and welfare of human subjects) (Lemmens & Freedman, 2000), internal IRBs pose other potential conflicts of interests (Freedman & McKinney, 2013), and opting for an external IRB affords a reasonable, even advisable, course of action.

Currently, funding for research with psychedelics has come from special-interest organizations (e.g., The U.K.-based Beckley Foundation, the non-for-profit Santa Fe, NM-based Heffter Research Institute, the California, SF-based Council on Spiritual Practices (CSP), and Santa Cruz-based MAPS), alongside more esoteric associations interested in human consciousness that may rely on crowdfunding and industry sponsorships (e.g., Merraki Institute). But this landscape appears in flux as private foundations with overlapping interests are edging closer to each other (e.g., the John Templeton Foundation and the Fetzer Institute). We expect that, before long, federal agencies will follow suit and call for psychedelic research proposals in the context of the larger rubric of the American National Institutes of Health (NIH and its subunits), the Canadian Institutes of Health Research (CIHR) (e.g., through mental health and neurological science), the National Science Foundation (NSF) in the U.S., the Canadian Social Sciences and Humanities Research (SSHRC), and the Canadian Natural Sciences and Engineering Research Council (NSERC).

5. Conclusion and Future Directions

Microdosing affords a unique opportunity to probe fundamental questions in cognition, consciousness, mental health, brain plasticity, and belief formation. Microdosing also allows for a multitude of interesting exploratory research avenues, such as characterizing the effects, if any exist, on sleep architecture (e.g., reports of insomnia from Citizen Science); measures of functional brain complexity (e.g., the Perturbational Complexity Index (Casali et al., 2013; Casarotto et al., 2016; Gallimore, 2015) and other such proxies; and effects on social and group dynamics.

And yet, without more studies, the anecdotal and informal testimonials touting the benefits of microdosing remains just that -- anecdotal, informal, and understudied (Kuypers et al., 2019). Against the sentiment of Citizen Science reports claiming improvements in creativity, mood, and productivity, for the limited parameters investigated so far, double-blind protocols from both Citizen Science and laboratory trials seem to find no effects on mood and only effects on certain aspects of creativity, productivity, and concentration (Bershad et al., 2019; Branwen, 2012; Yanakieva et al., 2018).

We ought to more carefully study microdosing to better tease apart psychosocial effects from those instigated by the active chemical ingredients and to streamline the research process. We currently lack systematic investigation into domains spanning the potential effects of microdosing with different psychedelic substances (e.g., LSD compared with psilocybin); different routes of administration and drug preparations (e.g., intravenous, oral, brewed as a tea); how effects unfold across a time course to identify peaks and troughs (if any exist); and the basic psychophysics of perception and conflict processing (e.g., visual discrimination, color perception, auditory sensitivity, proprioceptive and vestibular awareness, cognition and executive function, etc.).

The cultural and clinical return of psychedelics is already here: leading universities are launching centers for the study of psychedelics, clinical trials are beginning to examine psychedelics as medical interventions for different patient groups, Grand Rounds speakers explicitly mention, rather than indirectly allude to, these substances, conference workshops discuss them, TED talks disseminate their virtues, and increasingly more individuals are self-experimenting with them (*A Study of Psilocybin for Major Depressive Disorder (MDD)*, 2019; Carey, 2019; Doblin, 2019; Kotler & Wheal, 2017; Pollan, 2018; Waldman, 2018; Wong, 2017). Not only are regulatory agencies across the world--with special attention to North America and Europe -- looking at and approving an increasing number of research protocols, a wave of decriminalization is washing over American and Canadian cities -- from Denver, Colorado to Oakland, California, with Berkeley set to vote on the same issue in the coming year. A step ahead, the state of Oregon is preparing to vote on whether to legalize psilocybin. In Vancouver, British Columbia, a well-known cannabis activist has opened a company selling mail-order mushrooms in a show of civil disobedience, hoping to inspire changes to psilocybin regulation in a similar manner to cannabis legalization (Ginder-Shaw, 2019; Woods, 2019). Discussions of psychedelics no longer remain within informal forums, blogs, anonymous posts, and podcasts. Instead, they are appearing in mainstream media, on Netflix, at prime time television, and within the pages of *New York Times* Best Sellers.

The convergence of cultural interest, scientific lacuna, and regulatory revision places the research promise of microdosing with psychedelics in a unique and topical nexus. In a way,

microdosing presents a kind, perhaps less-threatening entrée into this "brave new world," for the more conservative-minded. Whereas research with psychedelics is a complex terrain to navigate, both scientifically and administratively, microdosing offers a gentle introduction to systematically (re-)studying these substances.

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