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Genís Ona, José Carlos Bouso

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Potential safety, benefits, and influence of the placebo effect in microdosing psychedelic drugs: A systematic review

Genís Ona[a,b], José Carlos Bouso[a,b]*

[a]ICEERS – International Center for Ethnobotanical Education, Research, and Services, Barcelona, Spain.

[b]Universitat Rovira i Virgili, Medical Anthropology Research Center (MARC), Tarragona, Spain.

*Corresponding author: José Carlos Bouso, C/ Sepúlveda, 65 Bajos 2 – 08015, Barcelona, Spain. Phone number: 93 188 20 99. Mail: jcbouso@iceers.org

Highlights

- There is increased interest in microdosing with psychedelic drugs.
- The most frequent drugs used for microdosing are LSD and psilocybin.
- The main benefit of microdosing is its mood-enhancing effects.
- Adverse events were related to a worsening of psychiatric symptoms.

Abstract

Microdosing psychedelic drugs—that is, taking sub-behavioral doses of lysergic acid diethylamide (LSD) or psilocybin—is a growing practice in Western societies. Taken mainly for creative or mood-enhancing purposes, thousands of users are increasingly being exposed to **(micro)doses of psychedelic drugs**. In this systematic review, we searched the available evidence from human studies, focusing our results in **terms of** three main axes: efficacy, safety, and the influence of the placebo effect in microdosing practices. While the available evidence has some strengths (e.g. large sample sizes, robust methodologies) there are also remarkable limitations (e.g. gender bias, heterogeneity of dosing schedules and drugs used). Highly contradictory results have been found, showing both **the** benefits and detriments of microdosing in terms of mood, creative processes**, and** energy, among other **regards**. This review provides a general overview of the methods and approaches used, which **could** be useful for improving future studies.

Keywords: microdosing; psychedelic drugs; hallucinogens; LSD; psilocybin.

1. Introduction

The “psychedelic renaissance” (Kotler, 2010) that started in the mid-1990s brought about renewed academic interest not only in psychedelic drugs’ mechanisms of action (Calvey & Howells, 2018) but also their therapeutic potential (Reiff et al., 2020). T**he** investigation **of psychedelic drugs** in experimental settings has been accompanied by **increased usage, for various reasons**, by the general population. Of particular interest is the periodic use of very low doses of lysergic acid diethylamide (LSD), psilocybin, and other psychedelic drugs, a practice that is popularly known as “microdosing.”

In pharmacological research, microdosing is understood as an interesting strategy for testing new drugs that consists of “low exposure” or “Phase 0” clinical trials. Those trials are not designed to assess tolerability but to obtain mechanistic information, such as pharmacokinetics in plasma or in drug targets. For this purpose, doses of no greater than 100 µg (for small molecules) or 1/100th of the No Observed Adverse Effect Level (NOAEL) are used (Burt et al., 2016). This approach has little, if anything, to do with microdosing psychedelic drugs. In the latter case, very low doses of psychedelic drugs are commonly used (e.g. less than 25 µg in the case of LSD), so no psychoactive effects are observed and, therefore, there are no impairments to the normal functioning of the individual. However, the absence **of a** psychoactive effect does not mean a **total lack** of effects, since microdosing practitioners usually report mood-enhancing effects, improved creative thinking, and the relief of various psychological disorders, among other effects (Kuypers et al., 2019). Thus, although subtle, the effects of microdosing psychedelics are noticeable, in contrast to microdosing practices in pharmacological research.

Although using tiny amounts of psychedelic drugs was first proposed by the Swiss chemist Albert Hofmann, the discoverer of LSD (Horowitz, 1976), it was not until the 2010s that this practice spread globally (Anderson et al., 2019a). **This increased interest in microdosing was partly due to the** publication of *The Psychedelic Explorer's Guide: Safe, Therapeutic, and Sacred Journeys* (Fadiman, 2011), in which Fadiman discussed the results of early experiments involving microdoses of psychedelic drugs. Additionally, some press articles appeared about workers in Silicon Valley using microdosing to enhance their creative abilities and efficiency (Glatter, 2015; Sahakian et al., 2018). As more people tried LSD and psilocybin microdosing, it seems that others started to take microdoses of ayahuasca or ibogaine, among other substances. Indeed, there are websites where one can read "protocols" for microdosing **with** these substances (The Third Wave, 2020). Given this growing trend, more research is urgently needed in this field in order to assess the safety of this practice and the potential risks it might pose to public health.

Beyond potential risks, the possible benefits of psychedelic microdosing should also be assessed. There is evidence that psilocybin, ibogaine, and other psychedelic drugs enhance neural plasticity and neurogenesis through their action on 5-HT_{2A} receptors (Ly et al., 2018). In fact, in recent years these substances have been termed "psychoplastogens" in order to emphasize this remarkable ability (Benko & Vranková, 2020; Dunlap et al., 2020; Ly et al., 2018). The "psychoplastogenic" effect of these substances, including ibogaine especially, along with their neuroprotective and neurotrophic-enhancing effects (Marton et al., 2019), are relevant in relation to neurodegenerative diseases. Preclinical research and anecdotal cases have suggested

that microdoses of ibogaine may be effective in reducing Parkinson's disease (PD) symptoms (Marton et al., 2019; European Ibogaine Forum, 2017). Other studies have started to **expose elderly individuals** to low doses of LSD in order to explore the safety of psychedelic drugs for the treatment of neuroinflammation associated with neurodegenerative diseases (Family et al., 2020). Due to the lack of effective treatments for neurodegenerative diseases, this area of study should be explored in depth.

With the aim of summarizing the current evidence on microdosing and therefore helping to facilitate future studies, we present a systematic review exploring central concerns, such as: the safety of microdosing, main reported benefits, and what aspects of these benefits might be attributed to a placebo effect. Additionally, the limitations of the available evidence and directions for future research are discussed.

2. Method

2.1. Search strategy

We conducted a search using the electronic databases PubMed, Scopus, and Web of Science, using the terms "psychedelics," "hallucinogens," "lysergic acid diethylamide," "psilocybin," "ibogaine," and "microdosing." These terms were combined using "AND" or "OR". Manual searches were also conducted using Google Scholar and Core (core.ac.uk) to identify other relevant studies.

2.2. Selection criteria and study selection

In order to find all of the relevant research published on the safety of microdosing, its reported benefits, and the possible influence of a placebo effect, the main eligibility criteria were: 1) publication in a peer-reviewed journal, and 2) studies in which microdosing practices were assessed in humans using either a qualitative or quantitative approach.

2.3. Recorded variables, data extraction and analysis

Recorded variables included author(s), year of publication, sample size, study location (country), study design, questionnaires used, microdosing protocol (if any), drug type and dose (if any), and main findings.

3. Results

The search of the literature yielded 64 separate references that were reviewed by abstract screening (first pass). Following the first pass and after excluding duplicates, 22 potentially relevant references were identified. Full-text reports of these citations were obtained for more detailed evaluation. Following detailed examination of the reports, 17 citations were finally included in the systematic review (Anderson et al., 2019a; Anderson et al., 2019b; Andersson & Kjellgren, 2019; Bershad et al., 2019; Bershad et al., 2020; Cameron et al., 2020; Fadiman & Korb, 2019; **Family et al., 2020;** Johnstad, 2018; Hutten et al., 2019a; Hutten et al., 2019b; Lea et al., 2020; Polito & Stevenson, 2019; Prochazkova et al., 2018; Rosenbaum et al., 2020; Webb et al., 2019; Yanakieva et al., 2019). See Figure 1 for a flow diagram of the selection process.

The included studies are comprised of 10 observational studies (Anderson et al., 2019a; Anderson et al., 2019b; Cameron et al., 2020; Fadiman & Korb, 2019; Hutten et al., 2019a; Hutten et al., 2019b; Lea et al., 2020; Polito & Stevenson, 2019; Prochazkova et al., 2018; Rosenbaum et al., 2020); three qualitative studies (Andersson & Kjellgren, 2019; Johnstad, 2018; Webb et al., 2019); and four randomized, double-blind, placebo-controlled clinical trials (Bershad et al., 2019; Bershad et al., 2020; **Family et al., 2020**; Yanakieva et al., 2019). The drugs most frequently used in this research were LSD and psilocybin. Although much less common, other drugs, such as cannabis, 1P-LSD, and mescaline have also been reported on in some of the included studies. See Table 1.

3.1. Sample

Considering all of the studies selected for inclusion in this review, the practice of microdosing was assessed among a total sample of 3,619 individuals. The preliminary report by Fadiman and Korb (2019) did not specify an exact sample size, since data collection is ongoing. Most samples were gender skewed, with more men than women, so that 69% of the total of 3,619 people was male. The gender ratio was only balanced in clinical trials, where the proportion of males was 40% (Bershad et al., 2019), 50% (Bershad et al., 2020), and 56% (Family et al., 2020; Yanakieva et al., 2019). Although the study by Family et al. (2020) and Yanakieva et al. (2019) recruited an elderly sample (mean age was 62.9 years), the other included studies selected young people between 18 and 35 years of age (mean age was 28.3 years). It must be noted that, since most of the studies used online-surveys to collect data, an unknown number of participants may have participated in multiple studies.

3.2. Benefits of microdosing

A study by Andersson and Kjellgren (2019) qualitatively analyzed videos posted on YouTube by individuals who microdosed (using mostly LSD and psilocybin, but also 1P-LSD and O-Acetylpsilocin [4-ACO-DMT]) in which they explained their experiences. Various benefits were reported. They were classified in four categories: 1) enhanced states and heightened senses (more focus; improvement in experiencing the present moment; improved mood; more energy; reductions in stress, sadness, or anger); 2) insights and transformation (augmented self-reflection; thoughtful insights; psycho-spiritual changes; improvements in personal orientation, priorities, and habits; improvements in self-confidence and self-acceptance; increased sense of empathy and deeper connections in personal relationships; a sense of reconnecting with nature; greater motivation to exercise, eat healthier food, and less habitually use social media; reduced procrastination; and spontaneous impulses to clean the house, tidy drawers, and pay bills); 3) improved abilities and optimal performance (increased creativity; enhanced productivity and effectiveness, especially in cognitively intensive jobs such as software development and music composition; heightened sense of presence, extraversion, attendance, and persuasiveness in social situations); and 4) relief and cure for health conditions (users reported benefits regarding depression, anxiety, post-traumatic stress disorder [PTSD], bipolar disorder, addiction, attention deficit and hyperactivity disorder [ADHD], autism spectrum disorder, paralysis from spinal cord injuries, dyspraxia, and cluster headaches).

Survey studies were the most fruitful in terms of revealing potential benefits. Anderson et al. (2019a) conducted a retrospective survey study that recruited 278

microdosing users of LSD and psilocybin. The main benefits reported were with regards to improved mood (26.6%), improved focus (14.8%), creativity (12.9%), self-efficacy (11.3%), and improved energy (10.5%). Participants also reported a reduction in the use of caffeine (44.2%), alcohol (42.3%), cannabis (30.3%), tobacco (21%), psychiatric prescription medications (16.9%), and illicit substances (16.1%). Cameron et al. (2020) designed an online-survey to collect data from microdosing practitioners. Users mainly microdosed with LSD and psilocybin (but also cannabis, ***N*,*N*-dimethyltryptamine or** DMT, and 3,4-methylenedioxymethamphetamine [MDMA]) and the main benefits reported were related to improvements in symptoms of depression (71.8%) and anxiety (56.5%), as well as improvements in memory (38.8%), attention (59%), and sociability (66.5%). Lea et al. (2020) conducted an international survey and created a sub-sample to examine the results of individuals who reported having microdosed. The main benefits (among these microdosing practitioners who mainly used psilocybin, LSD, and 1P-LSD) were improved mood and reduced anxiety, enhanced connectivity to people and the environment, and enhanced cognition. A different study by Anderson et al. (2019b) recruited individuals who microdosed through an on-line forum to test previously defined hypotheses. They found that microdosing predicted lower scores for dysfunctional attitudes and negative emotionality, and higher scores for wisdom, open-mindedness, and creativity. Hutten et al. (2019b) used an online-survey in order to recruit microdosing practitioners (who mainly used LSD, psilocybin, and MDMA) who had been diagnosed with physical and/or psychological disorders. The study measured the self-rated effectiveness of microdosing for the treatment of various conditions. In general, microdosing was rated as more effective than conventional medications, especially regarding anxiety, ADHD, and pain. Polito and Stevenson (2019) **conducted**

the only prospective, observational study with a sample of microdosing practitioners who were recruited through on-line platforms. Participants used mainly LSD and psilocybin. Baseline, daily, and long-term measures were used. Daily measures showed an increase for all scores (connected, contemplative, creative, focused, happy, productive, well) on days when users microdosed. Long-term improvements (at 6 weeks) were reported for depression and stress. Scores for the scale measuring mind-wandering decreased, while scores for the absorption scale increased during the study period.

Webb et al. (2019) and Johnstad (2018) performed individual interviews with microdosing users. Webb et al. (2019) recruited microdosing practitioners (who used LSD, 1P-LSD, and psilocybin) through social media and interviewed them by telephone. The main benefits that users reported were enhanced mood, increased productivity and creativity, and heightened sociability. Johnstad (2018) conducted individual interviews with participants who microdosed (mainly using LSD and psilocybin) and who were recruited through on-line forums. The main benefits reported were with regards to depression, anxiety, obsessive-compulsive disorder (OCD), PTSD, narcolepsy, migraine symptoms, and pain. Additionally, enhancements in energy, mood, and cognition were also reported.

Prochazkova et al. (2018) conducted a quasi-experimental study in which assessed creativity and intelligence among users under the effects of microdoses of psilocybin truffles. Improvements in both convergent and divergent thinking were reported. However, this study has important limitations, as subjects performed the same test

before microdosing and while under its effects, so a learning effect could have biased the results.

The published randomized, placebo-controlled studies did not specifically assess the potential benefits of microdoses, as they were primarily designed to assess safety and tolerability. However, some scales regarding changes in mood or drug effects were also included. Bershad et al. (2019) conducted a **clinical trial** involving microdoses of LSD (6.5, 13, and 26 μg) and a placebo. Microdosing LSD dose-dependently increased participant scores for the scales measuring experience of unity and blissful state, as measured by the 5D-ASC questionnaire. **Another study conducted by the same group (Bershad et al., 2020) reported small and inconsistent mood enhancements using 13 μg of LSD.**

3.3. Safety of microdosing

Anderson et al. (2019a) note that study participants reported several safety concerns. The authors classified them into 11 categories: illegality (29.5%; leading to unknown dosages, purity concerns, social stigma, etc.), physiological discomfort (18%; disrupted senses, temperature dysregulation, numbing/tingling, insomnia, gastrointestinal distress, reduced appetite, and increased migraines and/or headaches), impaired focus (8.8%; poor focus, distractibility, and absent-mindedness), increased anxiety (6.7%; general, social, and existential), impaired energy (7.2%; restlessness, fatigue, drowsiness, brain fog), impaired mood (6.9%; sadness, discontent, irritability, over-emotionality, mood swings, fear, feeling unusual), social interference (2.6%; awkwardness, oversharing, difficulties with sentence-production in social settings),

cognitive interference (2.3%; confusion, disorientation, racing thoughts, and poor memory), self-interference (1.2%; dissociation, depersonalization, rumination, over-analysis), increased symptoms (6.2%; participants reported concerns regarding psychological dependence, substance tolerance, hangover, and adverse psychological events), and others (10.6%; substance-related concerns regarding taste, pupil dilation, duration of effects, and negative drug interactions). Andersson and Kjellgren (2019) explain that some users experienced increased anxiety, panic attacks, physical and gastrointestinal discomfort, cramping, increased body temperature, restlessness, "jitters," over-stimulation (especially when using LSD), insomnia, impulsivity, reduced practical or problem-solving skills, and decreased cognitive performance. Cameron et al. (2020) found that 4.75% of participants experienced a worsening of their depression symptoms, 13.1% of their anxiety symptoms, 14.6% of their memory, 14.7% of their focus/attention, and 11.1% of their social abilities. They also noted that among the free-form responses regarding physical changes, 31.25% reported negative outcomes, such as occasional "swimmy" vision and sweats. Although Fadiman and Korb (2019) provided only anecdotal reports as preliminary results, they mentioned insomnia, uncomfortable physical symptoms, and increased anxiety as common adverse events that follow microdosing. Johnstad (2018) reported that some participants experienced a worsening of conditions or symptoms, including hangovers and mental health problems (unspecified). Other adverse events included insomnia, over-stimulation, and a "bad trip" when an LSD microdose was combined with cannabis. Hutten et al. (2019a) reported that one-fifth of their sample experienced negative effects, including both physical and psychological effects, but the effects are not specified. Lea et al. (2020) asked participants to report unwanted effects that occur often/always or at any point in

their lifetimes. Regarding occasional unwanted effects, the most common were difficulty concentrating, insomnia, symptoms of anxiety, feelings overwhelmed, and irritability. In contrast, frequent unwanted effects reportedly included insomnia; over-stimulation; undesired thoughts, emotions, and memories; anxiety; and muscle/joint pain. Polito and Stevenson (2019) found increased neuroticism, indicating that participants tended to experience more negative emotions after microdosing.

Regarding the clinical trials, Bershad et al. (2019) found increased anxiety among participants who took 26 µg of LSD relative to those who took a placebo, but not at lower doses. A different study by Bershad et al. (2020) reported significant increases in blood pressure following the administration of 13 µg of LSD as compared to placebo. Family et al. (2020) reported a higher frequency of headaches in the group that received LSD than in the placebo group.

3.4. Possible placebo effect

Only three placebo-controlled studies were found among the search results. Bershad et al. (2019) found that the LSD condition (13 and 26 µg, but not 6.5 µg) increased ratings for “feel drug” on the Drug Effects Questionnaire. The LSD-26 µg condition also increased ratings for “feel high” and “like drug”. LSD (13 and 26 µg) was associated with a higher systolic blood pressure, as it was 105.35 mmHg among those who took a placebo, as compared to 111.5 mmHg at 13 µg of LSD and 115.3 mmHg at 26 µg, and 26 µg significantly increased diastolic blood pressure as well. To summarize, 13 and 26 µg of LSD produced measurable subjective and physiological effects, which were linearly dose related. Bershad et al. (2020) found that, when given a placebo, 16 out of 20

participants correctly identified the substance as a placebo. When given LSD (13 µg), eight participants identified the substance as a placebo, seven as a sedative, one as a stimulant, one as an opioid, one as a cannabinoid, one was unsure, and only one subject identified it as a psychedelic drug. Near-significance increases were reported on Drug Effects Questionnaire (DEQ) ratings for "feel high," "want more," and "like drug," as well as regarding the sedation scale of the Addiction Research Center Inventory (ARCI). Yanakieva et al. (2019) recruited older adults. Using four different conditions (placebo, 5, 10, and 20 µg of LSD), no significant differences were found regarding subjective effects, despite the authors reporting "numerical tendencies" for drug effects in the LSD conditions. Although LSD did not produce relevant subjective effects as indicated by self-report measures, participants showed longer reproduction times in the temporal reproduction task when under the effect of LSD, in contrast to the placebo condition. Thus, the differential temporal reproduction performance across conditions was independent of self-reported drug effects. **Family et al. (2020) observed a statistically significant linear relationship between a sub-scale of the 5D-ASC questionnaire, three VAS, and the dose used, as the scores increased with increasingly high doses**.

4. Discussion

This systematic review collected the available evidence regarding microdosing, a growing practice regarding which there are still many unanswered questions. We were interested in providing information regarding three main issues: safety concerns, potential benefits, and the possible influence of the placebo effect. We found three types of studies: observational studies (n=10) mainly conducted through on-line surveys;

qualitative studies (n=3) for which data collected on-line or personal interviews were analyzed; and randomized, placebo-controlled clinical trials (n= 4).

While clinical trials are scarce in this area, the strength of the data provided by observational studies is remarkable. These studies were conducted in the period 2017-2020, some of them using very complex and robust methodologies in order to control as many variables as possible. One example is the study by Polito and Stevenson (2019) in which the effect of expectation was controlled for. Additionally, these observational studies provide data collected from a sample of over 3000 people who tried microdosing in a naturalistic setting, giving these results high external validity. This is a much larger sample than Phase-I and Phase-II clinical trials commonly use. In fact, the available clinical trials have some limitations. Participants in studies conducted by Bershad et al. (2019) and Bershad et al. (2020) who had previous adverse reactions to psychedelic drugs were excluded, so the results of these studies regarding the safety of microdosing are clearly biased. Additionally, they allowed participants to smoke and drink coffee before and after the studies' experimental sessions, although the effects of caffeine and nicotine could mask some of the subtle effects of microdosing.

Among the studies reviewed, the most frequently reported benefit was mood enhancement (Anderson et al., 2019a; Anderson et al., 2019b; Andersson & Kjellgren, 2019; Cameron et al., 2020; Johnstad, 2018; Lea et al., 2020; Webb et al., 2019). In some studies, related concepts regarding mood enhancement suggest mechanisms that might underlie such an effect. For instance, Andersson and Kjellgren (2019) reported that microdosing produced personal and thoughtful insights, improvements in self-confidence and self-acceptance, deeper connections with other people and with nature,

and a qualitative improvement in the experience of the present moment, all of which might enhance mood as well. **This is in accordance with the promising results obtained using regular doses of psychedelic drugs, where improvements in mood and depressive symptoms have been considered the main benefits (Romeo et al., 2020). It seems plausible that the mechanisms underlying this mood-enhancement effect would be the same proposed in terms of regular doses of psychedelic drugs, which is to say, a 5-HT1A,2A,2C agonism and the subsequent glutamate release (Halberstadt, 2015). This is associated with neurogenesis and neuronal plasticity (Ly et al., 2018; Benko & Vranková, 2020; Dunlap et al., 2020). Some psychological processes have also been associated with the therapeutic outcomes of regular doses of psychedelic drugs, such as decentering, acceptance, and other mindfulness-related capacities (González et al., 2020; Soler et al., 2018,2016; Franquesa et al., 2018; Sampedro et al., 2017). Other studies found a correlation between the intensity or the quality of the psychedelic experience and the therapeutic efficacy of psychedelic drugs (Roseman et al., 2018). However, in this case there is no psychedelic experience at all and, thus, the effects of microdosing on mood suggest that the subjective experience might not be as relevant as previously thought.** Reductions in stress were also reported (Andersson & Kjellgren, 2019; Lea et al., 2020). It is remarkable that preclinical studies have been published regarding improvements in mood and anxiety among rodents following the administration of microdoses of DMT (Cameron et al., 2019). Bershad et al. (2020) provided preliminary evidence regarding the potential mechanisms involved. They found a dampening effect in terms of amygdala activity and connectivity following the acute administration of 13 µg of LSD, a finding consistent with results obtained using higher doses of LSD (Grimm et al., 2018; Kraehenmann et al., 2015; Mueller et al., 2017).

Given the associations between amygdala hyperreactivity and various psychological disorders (Groenewold et al., 2013), the effect of both microdoses and regular doses of psychedelic drugs on this region could partially explain reported mood enhancements. Another frequently reported benefit of microdosing was enhanced creativity (Anderson et al., 2019a; Anderson et al., 2019b; Andersson & Kjellgren, 2019; Lea et al., 2020; Prochazkova et al., 2018; Webb et al., 2019). Remarkably, contradictory findings were found between observational studies and the clinical trial performed by Bershad et al. (2019) in terms of both mood and creativity. While benefits in these areas were frequently reported by microdosing practitioners, Bershad et al. (2019) found that none of the LSD doses (6.5, 13, and 26 μg) modified mood nor convergent thinking, an aspect of creativity. Most of the observational studies collected data using online surveys, so evidence of improvements to mood and creativity was obtained through subjective reports. However, regarding creativity, an observational study involved the administration of validated measures in an open-label, naturalistic setting (Prochazkova et al., 2018). The authors found improvements in both convergent and divergent thinking among participants who microdosed and were under the effects of "magic truffles" (psilocybin). However, this study has several limitations, including the lack of a control group and a possible learning effect. In light of this, we can conclude that the evidence regarding improvements to mood and creativity is weak. **Notably, research suggests that regular doses of psychedelic drugs can increase some measures of creativity (Mason et al., 2019; Kuypers et al., 2016).**

Some studies included in the review also reported on microdosing in relation to various mental health conditions. Improvements were mainly reported with regards to

symptoms of depression (Andersson & Kjellgren, 2019; Cameron et al., 2020; Johnstad, 2018; Polito & Stevenson, 2019), anxiety (Andersson & Kjellgren, 2019; Cameron et al., 2020; Hutten et al., 2019b; Johnstad, 2018), PTSD (Andersson & Kjellgren, 2019; Johnstad, 2018), ADHD (Andersson & Kjellgren, 2019; Hutten et al., 2019b), pain (Johnstad, 2018; Hutten et al., 2019b), and cluster headaches (Andersson & Kjellgren, 2019; Johnstad, 2018). Other less commonly reported disorders regarding which microdosing offered benefits were autism spectrum disorder, paralysis from spinal cord injuries, dyspraxia, and narcolepsy (Andersson & Kjellgren, 2019; Johnstad, 2018). Improvements in mood disorders are in line with not only the previously mentioned benefits regarding mood and related aspects, but also with the preliminary results of ongoing research on psychedelic drugs at regular doses (Benko & Vranková, 2020). Other disorders, such as ADHD, or common symptoms like pain, merit further research in order to clarify the potential mechanisms at work. **In the case of pain, the use of regular doses of psychedelic drugs has also proven beneficial (Castellanos et al., 2020), with long-lasting analgesic effects reported in case reports (Ona & Troncoso, 2019).** Kyzar et al. (2017) noted how very small, sub-behavioral doses of 2,5-Dimethoxy-4-iodoamphetamine (DOI) are required to induce potent anti-inflammatory effects. The authors suggest that sub-behavioral doses of psychedelic drugs should be tested as potential treatments for asthma, cardiovascular disease, metabolic disorders, inflammatory bowel disease, and other widespread disorders related to inflammatory processes (Kyzar et al., 2017). Among the observational studies collected, several report the use of microdosing as a substitution for prescribed psychiatric medication (Anderson et al., 2019a; Lea et al., 2020; Webb et al., 2019). Indeed, some subjects reported that the effectiveness of microdosing (mainly with psilocybin and LSD) was greater than that

of conventional medications (Hutten et al., 2019b). Given their well-known lack of efficacy and the side effects associated with psychiatric medications, innovative strategies are needed in order to discover new treatments (Ona & Bouso, 2020). Therefore, the use of psychedelic drugs in both regular and microdoses should be further explored. Reduced use of caffeine, alcohol, cannabis, and tobacco was also associated with microdosing (Anderson et al., 2019a; Andersson & Kjellgren, 2019; Webb et al., 2019), and thus additional research on microdosing as a treatment for addictions is also suggested. **This is in accordance with lines of research where regular doses of various psychedelic drugs are employed (Winkelman, 2014).**

Regarding the safety of microdosing, a remarkable proportion of study participants reported adverse events. We can classify these adverse events, detailed above, into five categories. The most common category concerned negative effects on mood, including increased anxiety, sadness, irritability, and worsening of symptoms of depression. The second category concerns physical discomfort, including overstimulation, disrupted senses, and temperature dysregulation. The third category concerns adverse events related to cognitive functioning, such as distractibility, absent-mindedness, and decreased performance on cognitive tasks. The fourth category concerns mental health issues, including insomnia, dissociation, depersonalization, and rumination or over-analysis. The fifth and final category concerns impaired social skills, including feelings of awkwardness, oversharing, and difficulties with sentence production. The most commonly reported issues were increased anxiety and insomnia. Most of the studies did not provide percentages regarding the proportion of participants who reported these adverse effects. However, in the case of anxiety, Anderson et al. (2019a) found that 6.7%

of participants reported this effect, while Cameron et al. (2020) found this to be the case among 13.1% of their sample. A “bad trip” was also reported, involving a microdose of LSD that was combined with a regular dose of cannabis (Johnstad, 2018). This supports the need for further research, specifically regarding potential drug-drug interactions between microdoses and other psychedelic drugs, cannabis, and even prescribed medications, since it seems that psychoactive effects can be potentiated. Some of these adverse events might be explained by overdosing, where a small- to medium-sized dose was taken rather than a microdose. This is particularly likely given the small amounts required for microdosing. Regarding the worsening of anxiety and symptoms of depression, users should be extremely cautious when microdosing as a self-medication strategy, since undesired effects can occur and occasionally result in fatalities. The current evidence regarding the efficacy of psychedelic drugs to treat mood disorders comes from using regular doses, and the effect of small or microdoses in this regard is unknown. From a psychodynamic point of view, Grof (2005) has stated that medium-sized to large doses are preferable in psychotherapeutic settings. According to him, low doses of LSD and other psychedelic drugs can start an “emergence” process of material coming up from the unconscious, but these low doses are insufficient for the process to be completed. This would result, rather, in a kind of stagnation, in which symptoms of anxiety are common. According to both Hutton et al. (2019a) and Anderson et al. (2019a), one-fifth of microdosing practitioners experience some type of adverse event. Given this high proportion, practitioners should be cautioned. Despite the apparent safety of extremely low doses of psychedelic drugs, such doses can entail significant risks, so more controlled studies are necessary in order to elucidate their safety profiles. Additionally, appropriate risk-benefit assessments will need to be conducted not only

with samples recruited from a healthy population but also with people who have mental health conditions. Even when this information becomes available, we should remember that microdosing practitioners will be still exposed to the risk of overdosing and other uncertainties linked to informal markets. **This high frequency of adverse events contrasts with their scarcity in the clinical trials in which regular doses of psychedelic drugs are administered. Some authors suggest that those studies do not implement appropriate methods for reporting adverse events (Luoma et al., 2020). In addition, small samples where a relatively high number of participants had previous experience with psychedelic drugs (more than 50% of the sample in some studies; Griffiths et al., 2016; Ross et al., 2016; Gasser et al., 2014) could have masked the potential adverse events of these treatments. The selection of participants with previous experience in psychedelic drugs, who had not experienced serious adverse events before, might explain the absence of challenging experiences in experimental settings. However, we must not forget that the percentage of the general population that has used psychedelic drugs is anecdotal (EMCDDA, 2018), so the results obtained in these studies, where half of the sample previously used psychedelic drugs, may clearly lack external validity. Paradoxically, microdosing could provide clues about potential adverse events caused by regular doses of psychedelic drugs that have been overlooked in clinical trials.**

In recent years, it has been suggested that, given the small amounts of psychedelic drugs that are commonly used when microdosing, the alleged benefits could be attributed to a placebo effect (Kuypers et al., 2019). Only the four randomized, placebo-controlled trials (Bershad et al., 2019; Bershad et al., 2020; **Family et al., 2020**; Yanakieva et al.,

2019) could assess the potential influence of a placebo effect. In LSD sessions, Yanakieva et al. (2019) found a delayed time perception in the absence of self-rated effects on perception. This suggests that even when no psychoactive effects are shown there can be alterations in certain parameters, so the dose would have pharmacological effects. Bershad et al. (2019) found no differences in mood, cognition, nor physiological parameters, while subjects reported notable subjective effects. This again suggest that the desired effects of microdosing would not depend on the psychoactive effects, as the benefits in that case were not significant. Bershad et al. (2020) reported increases in various rating scales following the administration of 13 µg of LSD, suggesting that at least some subjects noticed psychoactive effects, although only one identified them as hallucinogenic. The four clinical trials used LSD in similar doses (5-20 µg, 6.5-26 µg, and 13 µg). Despite being preliminary, these studies suggest that individuals can avoid psychoactive effects that might disturb normal functioning by taking less than 20 µg of LSD, and obtain noticeable benefits as well. However, we should not forget that the mean age of the sample recruited by Yanakieva et al. (2019) and Family et al. (2020) was 62.9 years, as that study focused on elderly adults. This limits our ability to make comparisons between studies and the generalizability of the results. It should also be noted that, beyond the placebo effect, a nocebo effect in naïve subjects is also reasonably likely to exist, given the social stigma around and illegality of psychedelic drugs. **For instance, Family et al. (2020) found a higher number of adverse events in the placebo group. The authors suggested that participants may have had expectations about the adverse events associated with the drug, as they were told that LSD could be given in the study**. Further placebo-controlled studies should examine these hypotheses.

While more controlled clinical trials should be performed, more naturalistic, non-gender biased, prospective observational research, in which subjects are evaluated in-person, is also necessary in order to overcome the limitations of survey-based studies. As Anderson et al. (2019b) stated, intense positive experiences with a substance motivate individuals to use that substance in the future. Thus, microdosing practitioners who have previous experience with regular doses of psychedelic drugs may be especially motivated to try microdosing and may evaluate its benefits more positively. Researchers should be aware of this limitation and determine the safety and efficacy of microdosing by recruiting naïve users.

Microdosing with drugs other than LSD and psilocybin represents a novel, vast, and promising field of research. As stated above, anecdotal reports suggest that microdosing with ibogaine could be effective for the treatment of PD (European Ibogaine Forum, 2017), since it has been shown that ibogaine increases neurotrophic factors. Analogs with similar properties are also being explored (Gassaway et al., 2016). Notably, this potential use of ibogaine is gaining early support through preclinical research (Marton et al., 2019). Harmalines (compounds present in ayahuasca) have been shown to increase the proliferation of human neural progenitors (Dakic et al., 2016) and stimulate adult neurogenesis (Morales-García et al., 2017). Recently, the potential role of ayahuasca as a treatment for PD and other neurodegenerative diseases has been revived (Djamshidian et al., 2015; Fisher et al., 2018). DMT has also been shown to produce neurogenesis and neuroprotection in cell cultures (Berthoux et al., 2018). Using metabolomics, a recent study found that ayahuasca contains compounds with highly neuroprotective properties (Katchborian-Neto et al., 2020). Psilocybin also induces

neurogenesis, and it has been suggested that it is geroprotective (Catlow et al., 2013; Germann, 2020). Thus, a future clinical application of microdosing may be the treatment of neurodegenerative diseases, one of the greatest threats to public health (WHO, 2020). Microdosing non-psychedelic drugs such as suboxone has led to other successful results in terms of helping individuals to overcome opioid dependence (Caulfield et al., 2020). Thus, we may be witnessing the beginning of an entirely new paradigm in pharmacological research and therapy.

In most of studies included in this review, the majority of participants used LSD and psilocybin, although the use of other psychedelic and non-psychedelic drugs was also reported to a much lesser degree, adding complexity to the results. No differential or specific effects of these other drugs were reported, so future studies should assess the effects and safety profile of various drugs in order to offer reliable information for each of them. The doses used ranged from 5 to 50 µg of LSD and from 0.1 to 0.5 g of dried mushrooms (psilocybin). There were very heterogeneous samples and most of the participants in observational studies did not know the exact dose they were taking. Regarding the clinical trials, it should be noted that a dose of less than 20 µg of LSD would be recommended, but we are lacking clinical trials involving microdosing with psilocybin. The most commonly used protocol was the one developed by Fadiman (2011) of one day microdosing and two days off, but there were six studies in which the regimen was not specified, and eight others in which other schedules were followed. Future studies should explore the most common dose schedules and try to standardize this as much as possible. **In addition, future naturalistic, observational studies would benefit from the inclusion of technology in their methods, such as the use of mobile**

applications for recording data instantly and accurately. In the case of clinical trials, larger samples would be desirable, as well as the inclusion of variables potentially associated with the therapeutic outcomes of microdosing, such as psychological processes or neuronal plasticity. Additionally, psychometric questionnaires can be effectively combined with a battery of health indicators (Ona et al., 2019) in order to collect valuable and easily comparable data. The exploration of efficacy measures in patients with both physical and psychological conditions, as well as neurodegenerative diseases, is warranted. Furthermore, studies involving patients should compare the risk-benefit ratio with the current available medication.

Several contradictory results have been found regarding risks and benefits. For instance, it seems that while some people benefit from microdosing in terms of mood, creative processes, and energy, other people experience a worsening of these and other dimensions. Regarding the latter, apart from subjective reports from observational studies regarding impaired energy, Bershad et al. (2020) found an increase in sedation following the administration of 13 µg of LSD in a controlled setting. **These contradictory findings could be the result of the different study designs used. For instance, clinical trials are specifically designed to find small effects in controlled settings. However, paradoxically, these effects are commonly restricted to those settings, whereas the same intervention may produce distinct effects in the general population, which is why some clinical trials are regarded as having poor external validity. Observational methods, while controlling fewer variables and therefore being more subject to bias, have enhanced external validity. So, the effects observed when different methodological approaches are followed will always differ to some extent and, thus,**

should be understood as complementary (Rawlins, 2008). In this case, the influence of the environment could be crucial, since the observed effects in naturalistic settings could result from interactions between the drug and a stimulating environment. The large sample sizes used in survey studies can also facilitate a more extensive collection of microdosing effects. Most of these effects would be difficult to find in the small samples used in clinical trials. This point is especially critical given the usually subtle effects of microdosing. Psychometric questionnaires commonly used in clinical may also fail to record those elusive effects, while the qualitative methods used in observational studies may provide more in-depth information.

In addition, making comparisons between studies is challenging, since the various samples were only matched by age and show a remarkable gender bias, with males making up 69.5% of the total sample. The presence of gender bias in the observational but not the controlled studies might explain some of the differences observed between these different kinds of studies.

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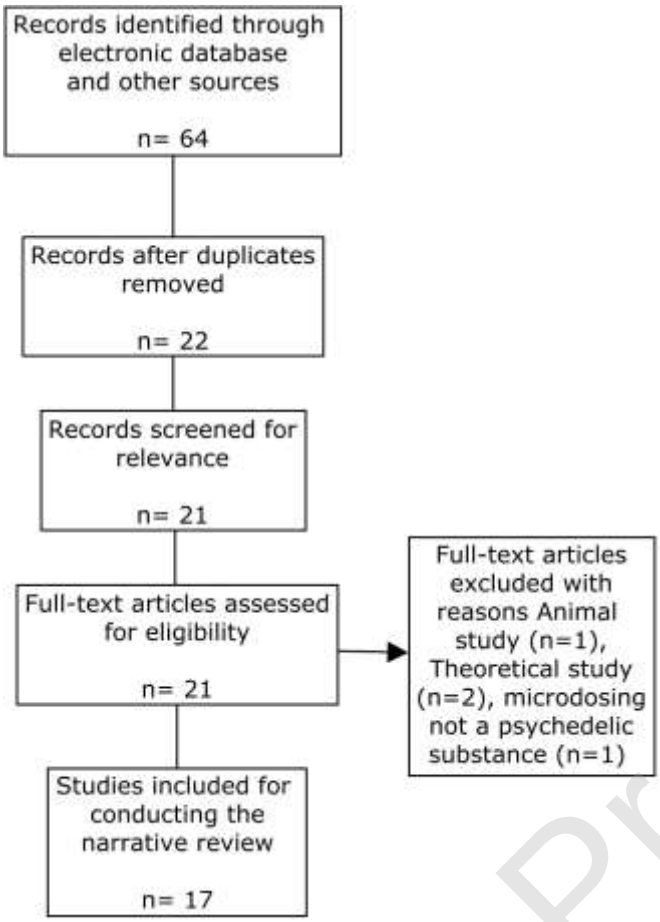
Fig.1



Author(s), publication year	Type of study (methodology)	Questionnaires used	Drugs assessed (dose)	Protocol used	Reported benefits	Reported adverse events
Anderson et al. (2019a)	Retrospective online survey	Survey (microdosing benefits, challenges, regimen, experienced improvements, reduced use of legal and illegal drugs, psychiatric medication).	LSD and psilocybin (NS)	NS	Improved mood (26.6%), improved focus (14.8%), more creativity (12.9%), self-efficacy (11.3%), improved energy (10.5%). Reduction in the use of caffeine (44.2%), tobacco (21%), cannabis (30.3%), psychiatric prescription medication (16.9%), and illicit substances (16.1%)	Physiological discomfort (18%), impaired focus (8.8%), increased anxiety (6.7%), impaired energy (7.2%), impaired mood (6.9%), social interference (2.6%), cognitive interference (2.3%), self-interference (1.2%), increased symptoms (6.2%)
Anderson et al. (2019b)	Retrospective online survey	BFI-2, Brief wisdom screening scale, DAS-A-17, Unusual uses task	LSD and psilocybin (NS)	NS	Lower scores in dysfunctional attitudes, negative emotionality, and higher scores on wisdom, open-mindedness, and creativity	NS
Andersson & Kjellgren (2019)	Qualitative analysis of Youtube videos (netnographic)	-	LSD, psilocybin, 1P-LSD, 4-ACO-DMT, DMT, ibogaine, mescaline, 2-CB, cannabis, 5-MeO-DALT (NS)	NS	Enhanced states and heightened senses, insights and transformation, improved abilities and optimal performance, and relief or cure for health conditions	Increased anxiety, panic attacks, physical and gastrointestinal discomfort, cramping, increased body temperature, restlessness, “jitters”, over-stimulating effects, insomnia, impulsivity, lessening of practical or problem-solving skills, decreased performance in cognitive tasks

Bershad et al. (2019a)	Randomized, double-blind, placebo-controlled clinical trial	Drug effects questionnaire, ARCI, POMS, 5D-ASC, Dual-n-back task, Digit symbol substitution task, the cyberball task, the emotional images task from the International Affective Picture System	LSD (6.5, 13, and 26 µg)	Single administration under double-blind condition	Higher scores in experience of unity and blissful state	Increased anxiety
Bershad et al. (**2020)**	Randomized, double-blind, placebo-controlled clinical trial	Drug effects questionnaire, ARCI, PANAS, 5D-ASC	LSD (13 µg)	Single administration under double-blind condition	NS	Increases in blood pressure
Cameron et al. (2020)	Retrospective online survey	Survey (familiarity with psychedelic microdosing, personal experience, which drugs used, changes perceived).	LSD, psilocybin, cannabis, DMT, MDMA (NS)	NS	Improvements in symptoms of depression (71.8%) and anxiety (56.5%), memory (38.8%), attention (59%), and sociability (66.5%)	Worsening of depression symptoms (4.75%), anxiety symptoms (13.1%), impaired memory (14.6%), impaired focus/attention (14.7%), impaired social abilities (11.1%). physical discomfort, including occasional 'swimmy' vision, bad memory, or sweats (31.25%)
Fadiman & Korb (2019)	Prospective online survey	NS	-	Microdosing on day 1, days 2 and 3 drug-free. This cycle is repeated at least for a month.	NS	Insomnia, uncomfortable physical symptoms, increased anxiety
Family et al. (2020)	**Randomized, double-blind, placebo-**	**CANTAB, RTI, PAL, RVP, SWM, VAS, DEQ, ARCI, 5D-ASC**	**LSD (5, 10, 20 µg)**	**Six administrations of the same assigned**	**NS**	**Headache**

	controlled clinical trial			**dose under double-blind condition**		
Johnstad (2018)	Qualitative analysis of individual interviews	Semi-structured interview	LSD, psilocybin, *Salvia divinorum*, *Amanita muscaria*, *Peganum harmala*, *Echinopsis pachanoi*, DMT, DOM, and cannabis (10-25 µg of LSD; 0.1-0.3 g dried mushrooms for psilocybin)	From every day to every fourth day	Improvements in symptoms of depression, anxiety, OCD, PTSD, narcolepsy, migraine symptoms, and pain. Enhancements in energy, mood, and cognition	Worsening of conditions or symptoms, including hangovers or mental health problems (unspecified). Insomnia, over-stimulation, "bad trip"
Hutten et al. (2019a)	Retrospective online survey	Survey (experience with regular doses of psychedelics and with microdosing, route of administration, frequency of use, where found microdosing schedule, motivation to microdose, motivation to stop using psychedelics, negative effects).	LSD, psilocybin, 1P-LSD, ayahuasca, NBOMe's, and 5-MeO-DMT (10 µg of LSD; 0.5 g dried mushrooms for psilocybin)	2-7 times a week	NS	One fifth of the sample experienced negative effects, both physical and psychological, but were not specified
Hutten et al. (2019b)	Retrospective online survey	Survey (psychedelic substance use history, mental and psychological diagnoses, effectiveness of conventional prescribed treatment, effectiveness of psychedelic self-medication).	LSD, psilocybin, 1P-LSD (NS)	NS	Effectiveness of microdosing rated higher than psychiatric medications in the case of anxiety, ADHD, and pain	NS
Lea et al. (2020)	Retrospective online survey	SDS and survey (which psychedelics were used, dosing schedules, duration of microdosing, dose adjustment,	LSD, psilocybin, 1P-LSD, DMT (0-50 µg of LSD; 0.1-0.5 g of truffles for	Most of the sample have been microdosing one day and two days off on a	Improved mood and anxiety, enhanced connection to people and environment, and enhanced cognitive abilities	Difficulties in concentration, insomnia, anxiety symptoms, feelings of overwhelming,

		obtaining psychedelics, knowledge sources, disclosure of microdosing to different groups, perceived benefits).	psilocybin; 8-9 mg for DMT)	repeated cycle (Fadiman)		irritability (occasionally experienced). Insomnia, over-stimulation, undesired thoughts, emotions or memories, anxiety, or muscle/joint pain (frequently experienced)
Polito & Stevenson (2019)	Observational, prospective study	Single rating for feelings of each of the following: Connectedness, contemplation, creativity, focus, happiness, productiveness, and wellbeing	LSD, psilocybin, mescaline (organic and synthetic), 4-HO-MET, DOB, 2C-C, 2C-D, 2C-E, LSA (13.5 µg of LSD; 0.3 g dried mushrooms for psilocybin; 2.6 g organic mescaline; 4 mg 4-HO-MET; 50 µg DOB; 10 mg synthetic mescaline; 50 mg 2C-C; 5 mg 2C-D; 3 mg 2C-E; 1.5 g LSA)	The mean time between doses was 6.7 days (range 1–34 days)	Increases in scores of connected, contemplative, creative, focused, happy, productive, well. Improvements in depression and stress at long-term	Increases in neuroticism
Prochazkova et al. (2018)	**Quasi-experimental**, pre-post study	Picture concept task, alternate uses task, Raven's progressive matrices	Psilocybin (0.37-0.41 g truffles)	Single ingestion of psilocybin truffles	Improvements in convergent and divergent thinking	NS
Rosenbaum et al. (2020)	Online survey, cross-sectional	Survey (microdosing regimen, substance use, psychiatric medication, and mental health history, dispositional personality).	LSD and psilocybin (13 µg LSD; 0.3 g dried mushrooms for psilocybin)	Most of the sample have been microdosing one day and two days off on a repeated cycle (Fadiman)	NS	NS

Webb et al. (2019)	Qualitative analysis of individual interviews	Semi-structured interview (procuring psychedelics, dosing schedules, benefits derived from microdosing)	LSD, psilocybin, 1P-LSD (0.2-0.5 g dried mushrooms for psilocybin)	NS	Enhanced mood, increased productivity and creativity, and heightened sociability	NS
Yanakieva et al. (2019)	Randomized, double-blind, placebo-controlled clinical trial	Temporal reproduction task, subjective drug effects through VAS	LSD (5, 10, and 20 µg)	Six single doses per participant (placebo, 5, 10, and 20 µg of LSD), every 3 days	NS	NS

Table 1. Overview of studies included in this narrative review. BFI-2= Big Five Inventory-2; DAS-A-17= Dysfunctional Attitudes Scale; ARCI= Addiction research center inventory; POMS= Profile of mood states; 5D-ASC= 5 Dimensions of Altered States of Consciousness Questionnaire; CANTAB= Cambridge Neuropsychological Test Automated Battery; RTI= Reaction time measures; PAL= Paired associates learning; RVP= Rapid visual information processing; SWM= Spatial working memory; PANAS= Positive and Negative Affect Schedule; NS= Non-specified; SDS= Survey of dependence scale; VAS= Visual Analogue Scale; LSD= Lysergic acid diethylamide; 1P-LSD= 1-propionyl-lysergic acid diethylamide; 4-ACO-DMT= O-Acetylpsilocin; DMT= *N*,*N*-dimethyltryptamine; 2-CB= 2,5-dimethoxy-4-bromophenethylamine; 5-MeO-DALT= *N*,*N*-di allyl-5-methoxy tryptamine; MDMA= 3,4-Methylenedioxymethamphetamine; DOM= 2,5-Dimethoxy-4-methylamphetamine; 5-MeO-DMT= 5-methoxy-N,N-dimethyltryptamine; 4-HO-MET= 4-hydroxy-N-methyl-N-ethyltryptamine; DOB= Dimethoxybromoamphetamine; 2C-C= 2-(4-Chloro-2,5-dimethoxyphenyl)ethan-1-amine; 2C-D= 2,5-dimethoxy-4-methylphenethylamine; LSA= d-lysergic acid amide;