Less is more? A review of psilocybin microdosing

General review article

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Abstract

Background: The applications of psilocybin, derived from “magic mushrooms” are vast, including a burgeoning practice known as microdosing, which refers to the administration of sub-hallucinogenic doses of psychedelic substances to obtain benefits without experiencing significant cognitive and perceptual distortion. However, current research is fairly new with several limitations and gaps that hinder adequate conclusions on its efficacy.

Aims: This semi-structured review aimed to identify and highlight research gaps in the field of psilocybin microdosing for future research.

Methods: A PRISMA-based strategy was employed, utilising a chain of keywords and key phrases across multiple databases, augmented by a cross-sectional Google search for relevant grey literature in the form of the top ten search results. A total of 40 studies and 8 unique websites were identified, summarised and tabulated into four distinct categories, namely non-clinical, clinical, observational and anecdotal evidence.

Results: The majority of available evidence originates from observational studies, while non-clinical and clinical study findings remain comparatively sparse and inconsistent. Web-based findings were consistent with current research findings. Key research gaps were highlighted: the imperative for more

randomised placebo-controlled trials, exploration of dose-response ranges, psychological and personality testing of participants, utilisation of active placebos, greater diversity in study populations, an increase in psilocybin-exclusive microdosing studies and the refinement of animal models.

Conclusion: Definitive conclusions regarding the efficacy of psilocybin microdosing remain elusive, emphasising the need for further study. Numerous research gaps necessitate consideration for future investigations.

Declaration of Interest: No conflicts of interest were present in the execution of this review.

Key words:

Psilocybin | Magic Mushrooms | Psychedelics | Microdosing | Sub-hallucinogenic

Introduction

Psychedelics are currently of great interest in psychiatry. These hallucinogenic substances are distinguished from other psychotropic drug classes by the cognitive and perceptual changes they induce (Konrath et al., 2021; Carlini and Maia, 2017). Despite their classification as Schedule 1 substances in 1967 and subsequent ban, the therapeutic potential of psychedelics such as psilocybin, lysergic acid diethylamide (LSD) and 3,4-Methylenedioxymethamphetamine (MDMA) has been extensively explored at acute, hallucinogenic doses over the last few years. (Nichols and Walter, 2020; Plesa and Petranker, 2022). Australia's recent change in scheduling to allow the use of MDMA and psilocybin to respectively treat post-traumatic stress disorder (PTSD) and treatment-resistant depression (TRD) alludes to the progress of this research (Care, 2023).

An emerging topic in psychedelic research is a practice known as microdosing. Microdosing refers to the administration of sub-hallucinogenic doses of a psychedelic substance - typically between one tenth and one twentieth of a standard dose – using a variety of dosing schedules to obtain subtle cognitive and emotional benefits without experiencing significant cognitive and perceptual distortion (Polito and Liknaitzky, 2022; Kuypers et al., 2019a). The practice is

commonly attributed to James Fadiman's 2011 book "The psychedelic explorer's guide: Safe, Therapeutic, and Sacred Journeys" (Fadiman, 2011). The attractiveness of microdosing as a strategy stems from the opportunity to gain therapeutic or maintenance mental health benefits without experiencing the profound cognitive changes associated with acute-dose psychedelic experiences (Rosenbaum et al., 2020). Additionally, the practice is easily adopted into a daily routine without the need for clinical supervision, making it a topic of interest not only in clinical research, but among the general public. This is particularly relevant within the context of the current global mental health burden. Common potential benefits reported by individuals who microdose include increased creativity, the daily moderation of anxiety and depression and general wellbeing (Polito and Liknaitzky, 2022; Rootman et al., 2022). Although microdosing is generally considered safe, unwanted side effects have been reported, such as anxiety and insomnia, the investigation of which is pertinent and on-going in prevailing research (Winstock et al., 2021).

A commonly used psychedelic in microdosing practices is psilocybin, the active ingredient of so-called "magic mushrooms" (Genís Ona, 2020). Psilocybin is a classic psychedelic that undergoes phosphorylation into its active metabolite, psilocin, which primarily targets and agonises brain 5-HT_{2A} receptors (Kolaczynska et al., 2021) [Figure 1].

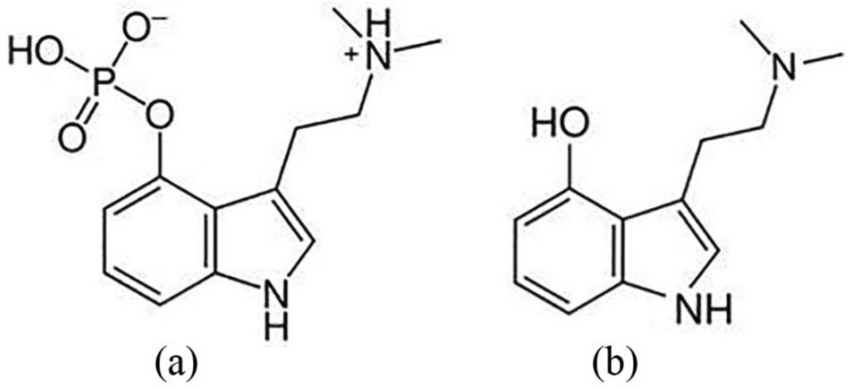


Figure 1: The chemical structures of (a) psilocybin and its active metabolite (b) psilocin (Kuypers et al., 2019b)

Psilocybin is an attractive option for microdosing due to its availability as a naturally expressed compound in various fungi expressing psilocybin and its derivatives, the majority of which are found in the *Psilocybe* genus (Van Court et al., 2022) [Figure 2]. Currently, there is substantial evidence supporting the effectiveness of high-dose psilocybin for treating end-of-life depression and anxiety in terminally ill patients, treatment-resistant depression (TRD) as well as obsessive-compulsive disorder (OCD) and substance use disorders including nicotine and alcohol (Yu et al., 2021; Grob et al., 2011; Carhart-Harris et al., 2016; Carhart-Harris et al., 2021; Goodwin et al., 2023; Raison et al., 2023; Kelmendi et al., 2022; Johnson et al., 2014; Bogenschutz et al., 2022).

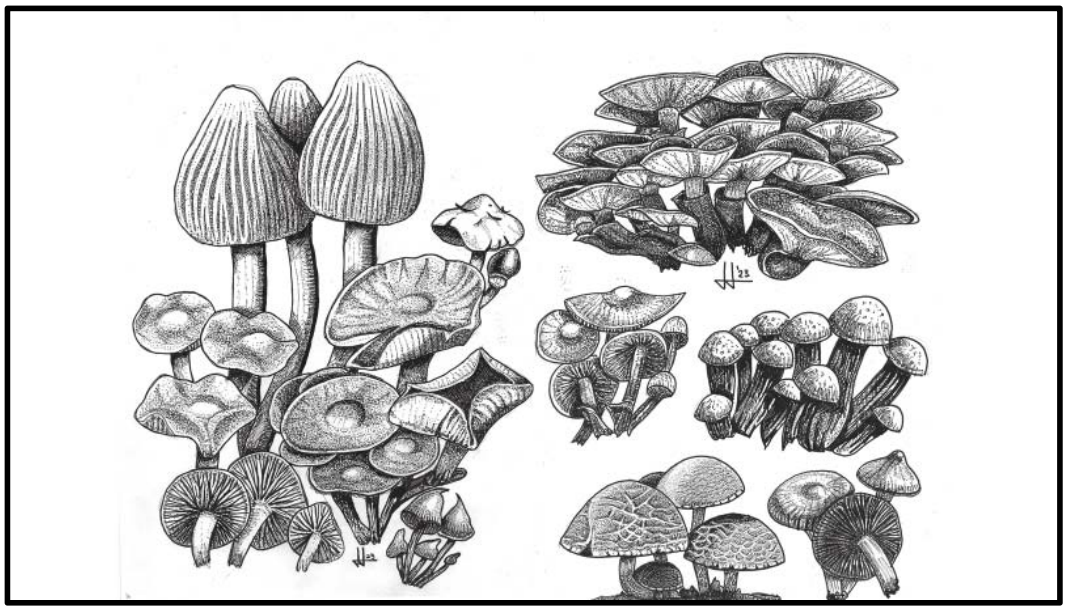


Figure 2: ***Left panel****: Genus Psilocybe (116 species) illustrating various forms of "ripening" to "decay" of species and strains, semilanceata, cubensis, cyanescens, hoogsagenii, and Mexicana.* ***Right panel****, from top to bottom and left to right: Genus Gymnopylus (14 species), Pholiotina (4 species), Copelandia (12 species), Galerina (1 species), and Inocybe (6 species) Pen and Ink drawing by L Laursen, Pretoria, September 2023. Used with artist's permission.*

However, unlike psychedelic-assisted therapeutic interventions with psilocybin, the investigation of psilocybin in microdosing practices is comparatively sparse. Disparity currently exists between anecdotal reports and more rigorous scientific research on the potential therapeutic outcomes of psilocybin microdosing. Limitations such as author epoch as well as a lack of well-designed studies

currently restrict pragmatic conclusions on microdosing practices (Golia, 2022). Additionally, there is a large inquiry into the involvement of placebo in microdosing outcomes (Polito and Liknaitzky, 2023). It is therefore desirable to gain a better understanding of prevailing research on psilocybin microdosing to advise on potential research gaps and minimise these limitations.

Methods

The aim of this review was to map the literature on microdosing with psilocybin in order to identify research gaps. This was achieved through several objectives, namely scoping published evidence on the definition of a microdose, dosing schedules, motives, outcomes as well as safety and efficacy.

Scientific, peer-reviewed studies were reviewed in a systematic manner. An additional, cross-sectional review of grey literature available on Google was conducted by screening the first 10 Google searches in order to explore the manner in which members of the public engage with microdosing information to incorporate the practice into their lifestyles. Investigating public-access information on microdosing was of value, as a large section of microdosing literature is derived from participants who have an established microdosing

practice.

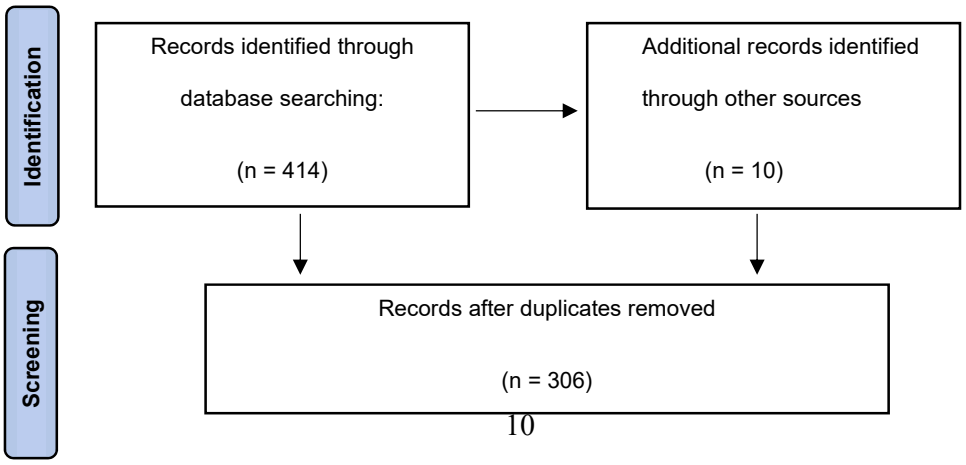
Chains of keywords and search terms were used with appropriate Boolean operators for the database search. A similar stream of operators was used to find applicable grey literature in the form of web searches on Google. These included (psilocybin OR magic mushrooms) AND (microdosing OR sub-hallucinogenic OR sub-perceptual). The databases utilised included EBSCOhost (APA PsycInfo, MEDLINE), PubMed, MEDLINE (Ovid) and Scopus. Search filters were applied to confine findings. All English full-text peer reviewed studies and applicable grey literature published since 1900 were eligible for inclusion in this review.

Article titles and abstracts were screened by two reviewers and critically evaluated for full-text studies concerning microdosing with psilocybin. Duplicates were deleted, after which exclusion criteria were applied to exclude systematic reviews, narrative reviews, meta-analyses and literature pertaining exclusively to acute hallucinogenic doses, thus ensuring that only primary evidence was considered. ‘Rayyan’, the web-based artificial intelligence application designed to assist researchers with structured reviews, was used to collect, de-duplicate and screen literature (Ouzzani et al., 2016; Harrison et al., 2020). Records not eligible were excluded with the following reasons: background article, wrong drug, non-microdosing-related outcome, wrong publication type and foreign language. EndNote 20 (Clarivate, London, UK) was used to catalogue citations and

references. Data from the eligible findings were extracted, summarised and tabulated. A meta-analysis was not conducted. No institutional ethics approval was required to conduct this review.

Results

A breakdown of the literature outlined during the selection process was compiled according to the guidance of the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) *(Figure 3).* A total of 414 records were initially identified. After de-duplication, 306 records and grey literature were screened for inclusion. Two-hundred and fifty-eight articles were excluded with reasons (*Figure 3*). Ultimately, a total of 40 studies and 8 Google searches were included in this review. Data were extracted, summarised and tabulated.



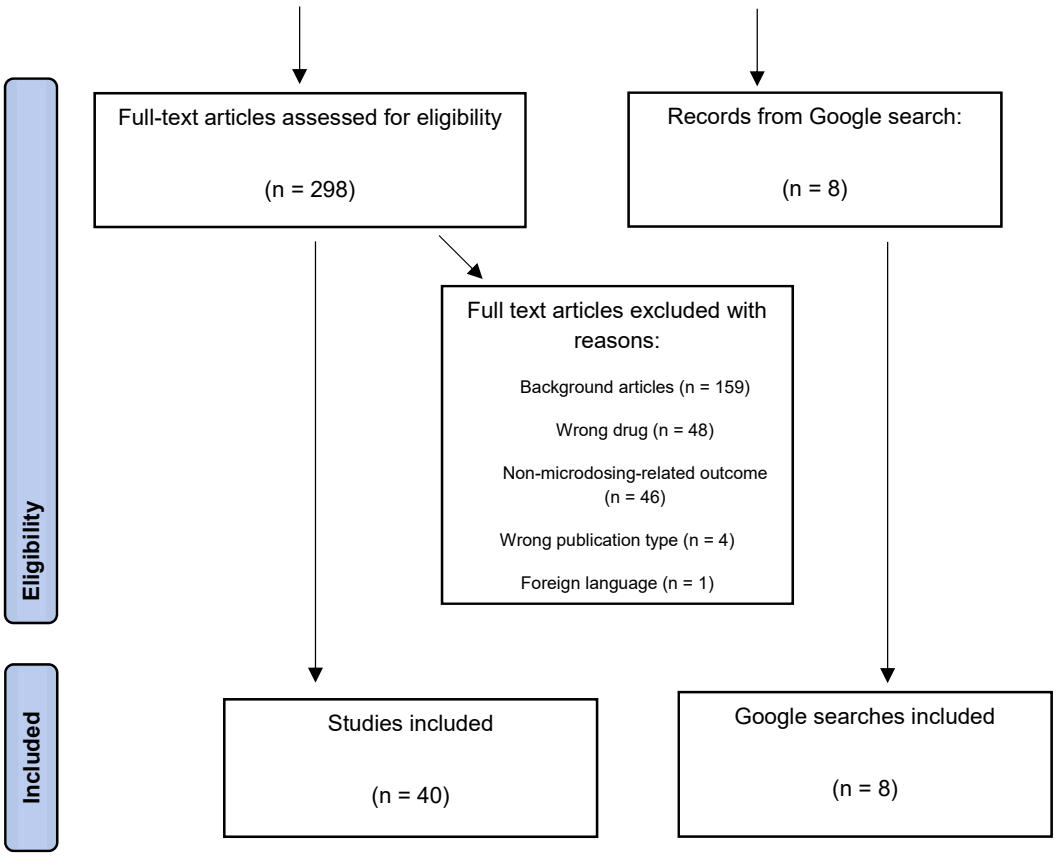


Figure 3: PRSIMA-guided flow diagram of the literature selection process.

Peer-reviewed literature

Tables 1, 2 and 3 summarise eligible peer-reviewed articles obtained through database searches. Extracted data were categorised as non-clinical (*Table 1*), clinical (human studies) (*Table 2*) and observational study findings (*Table 3*).

Despite the wide search criteria, studies were fairly recent, with the earliest considered publication date in 2006 and the subsequent majority of publication dates falling between 2018 and 2023. Additionally, the term “microdosing” was loosely defined across literature, with common underlying concepts broadly distinguishing the practice as regular administration of sub-hallucinogenic doses of psychedelic substances to achieve potential cognitive and emotional benefits. Doses were not standardised, but rather included a range of recorded doses.

Non-clinical studies

Results of experiments on animal models of disease often underscore the decision to conduct studies in humans. To this end, the relevance of rodent models in psilocybin studies has been extensively investigated in high dose studies (Shahar et al., 2022; Roberts et al., 2023; Hesselgrave et al., 2021). This contrasts with the relative lack of data in microdosing research (*Table 1*).

Non-clinical microdosing studies exclusively used rodent models and found limited evidence of the benefits of chronic low dose psilocybin administration. A total of 3 out of 6 studies investigated psilocybin microdosing exclusively. Various indications were investigated, including depression, anxiety, alcohol use disorder (AUD) and obesity. The use of animal models to investigate sub-hallucinogenic

doses was noted as a possible limitation to assessing efficacy in human studies and yet, further non-clinical studies were consistently recommended.

Table 1: Psilocybin microdosing: non-clinical (rodent) studies

Author	Title	Study design	Findings
R. R. Horsley; T. Páleníček; J. Kolin; K. Valeš (Horsley et al., 2018)	Psilocin and ketamine microdosing: Effects of subchronic intermittent microdoses in the elevated plus-maze in male Wistar rats	n = 40 Wistar rats Psilocin (n = 8): 0.05 /0.075 mg/kg (Saline placebo) Five minute elevated plus-maze (EPM) 48 hours after final dose	Modest anxiogenic effects, suggesting caution in therapeutic use of microdosing and highlighting the need for further research to confirm clinical relevance of findings Limitations noted: psilocin vehicle control group
M. W. Meinhardt; C. Güngör; I. Skorodumov *et al.* (Meinhardt et al., 2020)	Psilocybin and LSD have no long-lasting effects in an animal model of alcohol relapse	Alcohol deprivation effect (ADE) rat model: relapse-like drinking Acute dose & microdose	ADE model not supportive of psychedelic-reduced relapse behaviour: no long-term for male & female rats for both high & microdose regimes

G. A. Higgins; N. K. Carroll; M. Brown *et al.* (Higgins et al., 2021)	Low doses of psilocybin and ketamine enhance motivation and attention in poor performing rats: evidence for an antidepressant property	n = 30 male Long Evans rats Psilocybin (n = 15): 0.03 / 0.1 / 0.3 / 1 / 3 / 10 mg/kg (Saline placebo) 2 food motivated tasks: progressive ratio (PR) task; serial 5-choice (5-CSRT) task	Psilocybin & ketamine increase break point for food (PR task) & improve attentional accuracy & measure of impulsive action
N. Fadahunsi; J. Lund; A. W. Breum; C. V. Mathiesen *et al.* (Fadahunsi et al., 2022)	Acute and long-term effects of psilocybin on energy balance and feeding behavior in mice	Mouse model of obesity & binge-eating 3 groups of male C57BL/6J mice: wild-type; leptin-deficient ob/ob; melanocortin- 4 receptor knockout	0.3 mg/kg daily microdose & single 3 mg/kg acute dose did not induce metabolic/ behavioural changes in mouse model

		Psilocybin: 0.3 / 1 / 3 mg/kg (Saline placebo) Assess effects on energy expenditure & substrate utilisation	
J. Huang; M. Pham; W. J. Panenka; W. G. Honer; A. M. Barr (Huang et al., 2022)	Chronic treatment with Psilocybin decreases changes in body weight in a rodent model of obesity	Rat model of obesity n = 90 male, adult Sprague-Dawley rats Psilocybin: 0.1 / 1 / 5 mg/kg OR Metformin 300 mg/kg OR vehicle control	Modest anti-obesity effects of psilocybin, but greater efficacy demonstrated with metformin. Further investigation warranted. Limitations noted: natural weight gain of rat - plausible inaccuracy of weightless measures
H. I. Risca (Risca, 2022)	Pre-clinical behavioral assessment of chronic, intermittent low-dose psilocybin	n = 48 male Sprague-Dawley rats Psilocybin (IV): 0.025 / 0.05 / 0.1	No significant differences in any test between active vs control groups: lack of anxiolytic and antidepressant effects

	in rodent models of depression and anxiety	mg/kg OR control (saline) 3 tests for anxiolytic & antidepressant effects: light/dark conflict test, open field test, forced swim test	Limitations noted: doses may not be sub-perceptual; lack of positive control

Clinical trials

Clinical research progressed despite limited non-clinical evidence (*Table 2*). A total of 5 out of 8 studies investigated psilocybin microdosing exclusively. Results were mixed, lacking refined conclusions regarding the overall efficacy of psilocybin microdosing in a scientific setting. Participants across many studies broke placebo-blinding, which was frequently observed as a study limitation and further confounded the investigation of the role of placebo controls in microdosing. Findings were also not consistent with findings from observational studies (*Table 3*).

Table 2: Psilocybin microdosing: Clinical studies (human participants)			
Author	**Title**	**Study design**	**Findings**
F. A. Moreno; C. B. Wiegand; E. K. Taitano; P. L. Delgado (Moreno et al., 2006)	Safety, tolerability, and efficacy of psilocybin in 9 patients with obsessive-compulsive disorder	Randomised double-blind (no placebo) n = 9 DSM-IV defined OCD participants Up to 4 single doses of psilocybin ~1 week apart: very low = 25 µg/kg; low = 100 µg/kg; medium = 200 µg/kg; high = 300 µg/kg Overnight observation; Yale-Brown Obsessive Compulsive Scale (YBOCD) + visual analog scale to measure OCD symptoms at 0 / 4 / 24 hours after ingestion	Consistent decrease in OCD symptoms Very low & low doses were not as effective as medium & high doses in relieving symptoms

L. Prochazkova; D. P. Lippelt; L. S. Colzato *et al.* (Prochazkova et al., 2018)	Exploring the effect of microdosing psychedelics on creativity in an open-label natural setting	n = 38 microdosers from Psychedelic Society of the Netherlands (PSN) **Picture concept task** for convergent thinking; **alternative uses task** for divergent thinking; short version of **ravens progressive matrices task** for potential changes in fluid intelligence Test before and after **non-blinded** microdose (dry truffles): Low body weight: 0.22 g / Average body weight: 0.33 g / High body weight: 0.44 g	Convergent thinking & divergent thinking improvement, but fluid intelligence unaffected Speculation: psychedelics affect cognitive metacontrol policies via optimising balance of cognitive persistence and flexibility Limitations noted: lack of experimental control; lack of placebo condition; self-selection bias; possible effects of mood on divergent thinking task
B. Szigeti; L. Kartner; A. Blemings *et al.*	Self-blinding citizen science to explore	Self-blinding protocol: online instructions to incorporate placebo	No significant differences observed between active & placebo groups: both groups experienced

(Szigeti et al., 2021)	psychedelic microdosing	control into established microdosing regimes n = 191 (23% psilocybin) Psilocybin: 0.2 ± 0.12 g dry mushroom	improved psychological outcomes; placebo effect suggested Participants broke blind at a higher than random rate
M. van Elk; G. Fejer; P. Lempe; L. Prochazckova *et al.* (van Elk et al., 2022)	Effects of psilocybin microdosing on awe and aesthetic experiences: a preregistered field and lab-based study	Double-blind, placebo-controlled with 2-week crossover n = 30 Combined field- and lab-based study Self-administered psilocybin microdose vs placebo "Awe" measured with art-perception (response to short videos and abstract art)	Microdosing arm felt more awe compared to placebo arm Personalities with higher absorption positively relate to feelings of awe & art perception Strong expectations for microdosing benefits: could underline subjective benefits Majority of participants broke blind Recommendation: use active placebo

		(n = 28 for art perception study)	
E. Schindler; R. A. Sewell; C. H. Gottschalk *et al.* (Schindler et al., 2022)	Exploratory investigation of a patient-informed low-dose psilocybin pulse regimen in the suppression of cluster headache: Results from a randomized, double-blind, placebo-controlled trial	Randomised, double-blind, placebo-controlled study n = 14 for analysis (n = 16 randomised) 3 dosing sessions ~5 days apart Psilocybin: 0.143 mg/kg, OR placebo: microcrystalline cellulose) Participants maintained headache diaries	**Negative efficacy outcomes**: small sample size **Recommendations:** larger sample; define clinical effects in episodic & chronic participants; determine factors predicting treatment response; differentiate acute vs long-lasting effects
F. Cavanna; S. Muller; L. A. de la Fuente	Microdosing with psilocybin mushrooms: a double-blind	Double-blind placebo-controlled n = 34 participants starting to microdose	Acute effects significantly more intense for active (vs placebo), but ONLY for unblinded condition

(Cavanna et al., 2022)	placebo-controlled study	Psilocybin: 0.5 g dry *Psilocybe cubensis* mushrooms (Edible mushroom placebo)	EEG: reduced power in theta band; preserved levels for Lempel-Ziv broadband signal complexity Minor cognitive impairment reported Lack evidence for enhanced well-being/creativity cognitive function Expectation can contribute towards perceived benefits
C. Sanz; F. Cavanna; S. Muller *et al.* (Sanz et al., 2022)	Natural language signatures of psilocybin microdosing	Double-blind and placebo-controlled n = 34 Psilocybin: 0.5 g dry *Psilocybe cubensis* mushrooms	Microdosing arm: speech produced under acute effects of psilocybin microdoses (variables affected by higher doses): verbosity, sentiment

		Machine learning classifiers trained to distinguish between conditions (high accuracy, AUC ~0.8)	scores; no effect on semantic variability Low doses can be identified from unconstrained natural speech Potential for applicable, affordable, ecologically valid monitoring of microdosing schedules
J. Marschall; G. Fejer; P. Lempe *et al.* (Marschall et al., 2022)	Psilocybin microdosing does not affect emotion-related symptoms and processing: A preregistered field and lab-based study	Double-blind, placebo-controlled, within-subject crossover study n = 52 (sessions 1 & 3); n = 44 (sessions 2 & 4) Psilocybin: 0.7g dry Galindoi truffles (Non-psychoactive mushrooms & seeds placebo)	No effect on emotion processing/self-reported interoceptive awareness/anxiolytic or depressive symptoms of psilocybin microdosing vs placebo Participants broke blind in 2nd block Expectations had no effect

		Multidimensional Assessment of Interoceptive Awareness Questionnaire 1,5 hours after **2nd** dose Emotional go/no-go task & shortened Depression Anxiety Stress Scale completed 1,5 hours after **7th** dose	Recommendations: substance-naïve population; participants with clinical anxiety and depression

The randomised double-blind, placebo-controlled study design is a gold standard in drug testing; however, only 5 double-blind, placebo-controlled studies have investigated psilocybin microdosing. One study used a self-blinding protocol, whereby individuals who had already established the practice were provided a protocol to incorporate a placebo into their regimes (Szigeti et al., 2021). The majority of clinical-based studies investigated fixed doses, with two studies investigating doses relative to body weight: Prochazkova *et al.* examined three doses of dry mushroom according a low/average/high body weight, and Schindler *et al*. at a prescribed amount of 0.143 mg/kg of psilocybin (Prochazkova et al., 2018; Schindler et al., 2022). This is in stark contrast to

observational studies (*Table 3*) where doses were individualised according to participant preferences. Regular doses of dry mushroom that have been investigated clinically thus far range between 0.2 – 0.7 g.

Observational studies

The recreational use of psilocybin outside of formal scientific investigations has produced an abundance (n = 26) of observational evidence (*Table 3*). Common non-interventional study designs included interviews, online surveys, online questionnaires and case reports, with the majority of studies utilising online platforms. Perceived benefits, challenges and overall efficacy of microdosing were common study themes. Psilocybin microdoses were predominantly self-administered orally in dry mushroom form, with a few studies indicating psilocybin truffles (Lea et al., 2020b; Bornemann et al., 2021; Gotvaldová et al., 2021; Marschall et al., 2022). Dried and ground mushrooms were commonly prepared as capsules with doses ranging from 0.1 g – >1 g of dried mushroom.

A total of 5 studies out of 26 pertained exclusively to psilocybin, with the majority investigating microdosing as an overall practice. Psilocybin and LSD were the most frequently described psychedelic substances used in microdosing practices, however, not all studies could provide the exact psilocybin proportion. The predominant demographic of the majority of participants in these studies

was male Caucasians from middle-to-high income groups, principally from the United States of America (USA).

Table 3: Psilocybin microdosing: non-interventional observational studies

Author	Title	Study design	Findings
P. G. Johnstad (Johnstad, 2018)	Powerful substances in tiny amounts: An interview study of psychedelic microdosing	Online interview of n = 21 current/former microdosers (exact psilocybin number unknown) *Psilocybe cubensis* mushrooms: 0.1–0.3 g	**Perceived/reported benefits**: energy, mood, cognition - improved daily functioning; extraversion **Perceived challenges**: overdosing, potentiate alcohol effects, insomnia LSD more stimulating than psilocybin (positively and negatively perceived) Treatment vs enhancement not always clear

J. Fadiman; S. Korb (Fadiman and Korb, 2019)	Might microdosing psychedelics be safe and beneficial? An initial exploration	Microdosing self-study: microdosing protocol offered to interested participants (various ages, circumstances, diagnoses) n = >1000 (exact psilocybin number unknown) Protocol: dose on day 1, no dose on days 2 and 3; repeat for a month	**Positive self-report evidence**: improved feelings of depression, even with type I and II bipolar disorder depressive episodes (not manic episodes); improved productivity and creativity; improved patience; resilience to chronic pain (note: not necessarily relief, only mitigation); relief of neuropathic pain Possible alternative stimulant treatment to attention deficit disorders **Negative self-report evidence**: physical discomfort (usually on mushrooms); increased anxiety (most common)

T. Anderson; R. Petranker; A. Christopher *et al.* (Anderson et al., 2019a)	Psychedelic microdosing benefits and challenges: An empirical codebook	Cross-sectional, retrospective, anonymous online survey of n = 278 microdosers (n = 50 psilocybin only; n = 33 psilocybin & LSD)	**11 beneficial outcomes**: improved mood; improved focus; creativity; self-efficacy; improved energy; social benefits; cognitive benefits; reduced anxiety; physiological enhancement; other perceived benefits; reduced symptoms (other) **11 challenging outcomes**: illegality; physiological discomfort; impaired focus; increased anxiety; impaired energy; impaired mood; social interference; cognitive interference; self-interference; other perceived challenges;

			increased symptoms (other) Psilocybin-only microdosers report benefits as more important vs other users
T. Anderson; R. Petranker; D. Rosenbaum *et al.* (Anderson et al., 2019b)	Microdosing psychedelics: personality, mental health, and creativity differences in microdosers	Online questionnaire of n = 594 current/former microdosers (psilocybin = 28%) and n = 315 non-microdosing controls	Lower scores for dysfunctional attitudes, negative emotionality (vs controls) Higher scores for wisdom, open-mindedness, creativity (vs controls) Limitations noted: sample demographics predominantly Caucasian, middle-class, heterosexual males

M. Andersson; A. Kjellgren (Andersson and Kjellgren, 2019)	Twenty percent better with 20 micrograms? A qualitative study of psychedelic microdosing self-rapports and discussions on YouTube	Qualitative, inductive thematic analysis of YouTube videos & associated comments (exact psilocybin number unknown)	**8 themes identified**: microdosing motives, expectations and context; enhanced states and heightened senses; insights and transformation; improved abilities and optimal performance; relief and cure for health conditions; unwanted effects and lack of results; microdosing approaches, strategies and dosage; general viewpoints on microdosing Intention influenced outcome (positive and negative) Limitations noted (*eg, cannot account for placebo*)

N. R. P. W. Hutten; N. L. Mason; P. C. Dolder; K.P. C. Kuypers (Hutten et al., 2019a)	Motives and side-effects of microdosing with psychedelics among users	Online questionnaire of n = 1116 former/current microdosers (n = 645 psilocybin) Common psilocybin dose: 0.5 g mushroom (exact doses unknown)	**Motivation (in decreasing order of selection**): performance enhancement (increased energy, concentration & creativity etc), mood enhancement, symptom relief, curiosity and other **Negative effects**: psychological (eg, depression, anxiety, paranoia) more common than physical
N. R. P. W. Hutten; N. L. Mason; P. C. Dolder; K. P. C. Kuypers (Hutten et al., 2019b)	Self-rated effectiveness of microdosing with psychedelics for mental and physical health problems among microdosers	Online questionnaire of n = 410 microdosers (majority psilocybin, n = 355) **Odds ratios** calculated for comparison of self-rated effectiveness (SRE) of microdosing with psychedelics (MDP) for	**Odds ratio findings:** (1) SRE of MDP *higher* than conventional treatment/s for mental (ADHD/ADD/anxiety) AND physical disorders (2) SRE of MDP *lower* than regular doses for mental NOT physical

		mental AND physiological disorders against: (1) conventional treatment/s; (2) higher/regular doses	disorders (no difference shown)
M. Webb; H. Copes; P. S. Hendricks (Webb et al., 2019)	Narrative identity, rationality, and microdosing classic psychedelics	Semi-structured interviews of n = 30 microdosers (majority psilocybin, n = 13) on motives, experiences, practices/regimes, strategies Common psilocybin dose: 0.2 - 0.5 g mushroom every 3-4 days	**Motive**: self-improvement Microdosing perceived as part of health & wellness Participants preferred to buy substance from people they knew, or grow mushrooms themselves Common preparation: capsules
V. Polito, R. J. Stevenson (Polito and Stevenson, 2019)	A systematic study of microdosing psychedelics	**Study one:** observational investigation of n = 98 microdosers (n = 478 total reports; n = 225 psilocybin reports): daily ratings of psychological	**Study one:** increase in psychological functioning, absorption, neuroticism & decreased levels of depression, anxiety

		functioning (6 weeks); n= 63 psychometric measures (baseline vs end of study) **Study two:** investigate expectancy bias of n = 263 naïve & experienced microdosers (exact psilocybin amount unknown)	distractibility; residual effects limited **Study two:** discrepancy between naïve population beliefs vs limited observed outcomes of experienced microdosers
T. Lea; N. Amada; H. Jungaberle (Lea et al., 2020a)	Psychedelic microdosing: A subreddit analysis	Coding analysis of 174 threads on r/Microdosing subreddit Common psilocybin dose: ~0.1 - 0.6 g of dry/fresh mushroom Microdose = 5 - 20% of standard dose (psilocybin: 1-5 g) Common schedule: one day dose, next two days no dose (3 day cycle)	**Motivation**: self-management of mental health; improve psychosocial wellbeing; enhancing cognitive performance **Reported benefit**: enhanced cognition & creativity; reduced depression & anxiety; enhanced self-insight & mindfulness; improved mood & attitude;

			improved habits & health behaviours; improved social/inter-personal interactions; heightened sensation & perception **Limitations**: dosing issues; adverse physical effects; illicit nature of substances; limited/no mental health or cognitive improvement; increased anxiety; unpleasant "off" days (no dose days); short-term/mild benefits; concern for dependence/drug-related risks Limitations noted: sampling bias
D. Rosenbaum;	Microdosing psychedelics:	Anonymous online survey of n = 414 microdosers	**Odds ratio tests:** significantly lower odds

C. Weissman; T. Anderson *et al.* (Rosenbaum et al., 2020)	Demographics, practices, and psychiatric comorbidities	(25.9% psilocybin) & n = 315 non-microdosers (control) Exploratory odds ratio tests: demographic variables, rates of psychiatric diagnoses, past-year recreational substance use Common psilocybin dose: 0.3 g mushrooms	of religious affiliation; near-significantly higher odds of being male; not more likely to report psychiatric history; significantly lower odds of reporting SUD history/anxiety disorders; ~5x more likely to report recent substance use; 1.5x more likely to report past recreational substances use; significantly higher odds of full-dose classic psychedelic use **Characteristic differences:** No significant: age, sexual orientation, ethnic heritage, social class & highest completed formal

			education Significant: religion & gender Common regimen: one-day-on, two-days-off
T. Lea; N. Amada; H. Jungaberle; H. Schecke; M. Klein (Lea et al., 2020b)	Microdosing psychedelics: Motivations, subjective effects and harm reduction	Online survey of n = 525 microdosers (55% psilocybin as mushroom/truffle): 0.11 to 0.2 g (26.8%); up to 0.1 g (19.9%); 0.21 to 0.35 g (22.6%); 0.36 to 0.5 g (13.9%); > 0.5 g (12.2%); unknown (4.5%)	**Primary motivations**: improve mental health; personal development; cognitive enhancement **Perceived short-term benefits:** improved mood & anxiety; enhanced connection to others & environment; enhanced cognition **Negative/potentially unwanted effects:** stronger-than-expected psychedelic effects; anxiety-related effects; physical adverse effects (*eg,* stimulation)

			Common dosing schedule: one-day-on, two-days-off (31.8%) Common preparations: cutting dry mushroom/truffle into small pieces (29.6%); ground and put into capsules (22.0%); ground up only (20.9%)
T. Lea; N. Amada; H. Jungaberle *et al.* (Lea et al., 2020c)	Perceived outcomes of psychedelic microdosing as self-managed therapies for mental and substance use disorders	International online survey of n = 1102 current/past microdosers (psilocybin n = 511)	**Indication:** depression; anxiety; other mental disorders; substance use cessation/reduction **Perceived benefit:** improved mental health Multivariate analysis (range of variables): gender, education, microdosing duration & motivations, recent high doses

			Psilocybin microdosing: variable associated with motivation to improve mental health (vs LSD)
L. P. Cameron; A. Nazarian; D. E. Olson (Cameron et al., 2020)	Psychedelic Microdosing: Prevalence and Subjective Effects	Anonymous online survey of n = 2347 microdosers (n = 83 psilocybin)	Microdose = chronic, intermittent administration of sub-hallucinogenic doses of psychedelic compounds **Perceived outcome:** mood improvement; decreased anxiety; enhanced memory & attention & sociability **Frequent discontinuation motives:** risk (illegality); difficult procurement
J. M. Rootman; P. Kryskow; K. Harvey *et al.*	Adults who microdose psychedelics report health related	Cross-sectional data obtained anonymously via iPhone application from n = 4050 self-	**Motives**: enhance mindfulness (most common); improve mood; enhance

(Rootman et al., 2021)	motivations and lower levels of anxiety and depression compared to non-microdosers	selected microdosers (majority psilocybin, exact number unk) & n = 4653 non-microdosers (control) Psilocybin: low = ≤ 0.1 g; medium = 0.1–0.3 g; high ≥ 0.3 g	creativity; enhance learning Confirm prior research of positive associations between microdosing and mental health Reduced symptoms of depression, anxiety & stress among adults with reported mental health concerns
L. S. Kaertner; M. B. Steinborn; H. Kettner *et al.* (Kaertner et al., 2021)	Positive expectations predict improved mental-health outcomes linked to psychedelic microdosing	4-week online survey of n = 81 microdosers (~ 50% psilocybin use)	**Benefits:** improved psychological well-being & emotional stability; reduced anxiety & depression symptoms; increased psychological resilience, social connectedness, agreeableness, nature relatedness & aspects of psychological flexibility

			Positive expectation = positive outcome; suggestive of significant placebo response
J. Bornemann; J. B. Close; M. J. Spriggs *et al.* (Bornemann et al., 2021)	Self-Medication for Chronic Pain Using Classic Psychedelics: A Qualitative Investigation to Inform Future Research	1-h semi-structured discussion with thematic analysis of n = 11 microdosers (psilocybin: mushrooms (n = 9) & truffles (n = 2)) ***NOTE:*** *participants listed >1 option; numbers do not account for entire sample*	Positive impact of psilocybin microdosing on pain management; regained functionality reported for both macro- & microdoses Evaluation of micro- vs macrodosing differences difficult: "potentially discrete processes"
J. M. Rootman; M. Kiraga; P. Kryskow *et al.* (Rootman et al., 2022)	Psilocybin microdosers demonstrate greater observed improvements in mood and mental health at one month relative to	Naturalistic, observational study over of n = 953 microdosers & n = 180 non-microdosers	"Small- to medium-sized" mood/mental health improvements across sample Improvement in psychomotor

	non-microdosing controls		performance in older participants Combination of psilocybin with lion's mane mushrooms (*Hericium erinaceus*) & niacin (vitamin-B3) associated with psychomotor performance improvement
V. Bonnelle; W. J. Smith; N. L. Mason *et al.* (Bonnelle et al., 2022)	Analgesic potential of macrodoses and microdoses of classical psychedelics in chronic pain sufferers: a population survey	Online survey of n = 250 participants suffering chronic pain & have experience with microdosing/microdosing /both (psilocybin microdose n = 51)	Analgesic potential of microdosing for pain management (unrelated to mood improvements or advocacy associated with psychedelics) Microdosing induces less pain relief than macrodoses (note: macrodoses not

			commonly used for pain relief) Expectation bias noted
R. Petranker; T. Anderson; L. J. Maier *et al.* (Petranker et al., 2022)	Microdosing psychedelics: Subjective benefits and challenges, substance testing behavior, and the relevance of intention	n = 6753 responses from Global Drug Survey sub-section on microdosing (psilocybin n = 2832; psilocybin & LSD n = 862)	**Common benefits:** enhanced mood; creativity; focus; sociability **Common challenges:** "None" Majority of participants did not test substance before use Approach-intention predicted less benefits
V. Hartong and A. van Emmerik (Hartong and van Emmerik, 2022)	Psychedelic Microdosing, Mindfulness, and Anxiety: A Cross-Sectional Mediation Study	Cross-sectional study via anonymous online questionnaire administered to n = 497 current/former microdosers (psilocybin n = 208) & n = 234	Current & former microdosers vs control: lower STAI-T scores; associations with trait anxiety mediated by trait mindfulness NOTE: association of

		microdosing-naïve controls State-Trait Anxiety Inventory – Trait subscale (STAI-T): measure **trait anxiety** 5-item Five-Facet Mindfulness Questionnaire: measure **trait mindfulness**	microdosing & STAI-T scores **non-significant** when n = 386 participants with previous macrodosing experience excluded
K. Corrigan; M. Haran; C. McCandliss *et al.* (Corrigan et al., 2022)	Psychedelic perceptions: mental health service user attitudes to psilocybin therapy	Questionnaire administered to n = 99 mental health service users: demographics, diagnoses, previous psychedelic/other drug use, attitudes to psychedelics & psilocybin therapy	Majority support psilocybin research 20% view psychedelics as addictive/unsafe even under medical supervision **Factors demonstrating favourable attitudes towards psilocybin:** younger age; previous

			psychedelic experience; non-religious beliefs
A. Lyons (Lyons, 2022)	Self-administration of Psilocybin in the setting of treatment-resistant depression	Case report: 43-year-old white male; TRD (past medical history of hypertension & MDD) Psilocybin: 0.2 g dry, self-grown *P. cubensis* mushroom Self-administration following Fadiman protocol: dose one day, no-dose two days (3 year regime: 8 week cycle, 4 week break, restart 8 week cycle)	Hamilton Depression Rating Scale (HDRS) scores: 1 week after starting (3 doses) = 20; 6 months = 11; 2,5 years = 7 (depression in remission) Side effects: mild nausea after first 2 doses Limitations noted: small sample; lack of formal administration/dosing
D. A. Kinderlehrer (Kinderlehrer, 2023)	The effectiveness of microdosed Psilocybin in the treatment of neuropsychiatric	Case study: 70-year-old male; immunocompetent (serologically positive for neuropsychiatric Lyme disease); poor tolerance	Within 2 days: noticeable mood improvement; within 2 weeks: feeling consistently well; 2

	Lyme Disease: A Case Study	of antimicrobial/psychotropic medications Psilocybin: dry mushroom; initial 100 mg T.I.W.; increased to 125 mg 2 weeks later	years later: depression and anxiety in remission
R. S. Ryan; A. Copello; A. P. Fox (Ryan et al., 2023)	Experiences of microdosing psychedelics in an attempt to support wellbeing and mental health	Anonymous online, text-based, semi-structured interview of n = 13 microdosers (n = 5 psilocybin only; n = 1 psilocybin & LSD) Interpretive Phenomenological Analysis	**Theme 1 - seeking a solution: agency and rationale:** aspects of self-help; important decision, not recreational use **Theme 2 - microdosers as scientists:** investigate and implement in a scientific manner **Theme 3 - catalysing desirable and beneficial effects:** not considered curative,

			rather a catalyst/tool for learning and new behaviours
M. Lyes; K. Yang, J. Castellanos; T. Furnish (Lyes et al., 2023)	Microdosing psilocybin for chronic pain: a case series	Case series: chronic neuropathic pain management of n = 3 participants Psilocybin (self-administered): 250 mg for >6 months (50 mg occasionally); 500 mg daily for 7-10 days + rest 2-3 days (750 mg-1 g occasionally); 1000 mg every 6 to 8 weeks + exercise	Well-observed pain relief and analgesia + muscles spasms in quadriplegia case + complete pain remission in one case No tolerance development/rebound pain/withdrawal symptoms noted Limitations noted: small sample size; characteristics & patterns ungeneralisable; potential confounding effects on underlying psychiatric comorbidities; self-

			reported medical history; possibility of perceived stigma; placebo un-accounted for

These studies were mostly congruous for a favourable opinion of psilocybin microdosing, or microdosing as an overall practice. However, many were not exclusive to psilocybin. Rather, information formed part of studies investigating multiple substances such as LSD (commonly), or ketamine.

The majority of studies were anonymous investigations such as interviews, survey and questionnaires. Certain interviews and case reports provided more detailed participant information to elaborate on microdosing indications and outcomes (Johnstad, 2018; Webb et al., 2019; Kinderlehrer, 2023; Lyes et al., 2023).

The perceived benefits and challenges of microdosing were also commonly investigated themes. A variety of indications were described, such as obsessive compulsive disorder (OCD), depression (including TRD), neuropathic pain management and neuropsychiatric Lyme disease. Themes of mindfulness and intention were also investigated. This laid the groundwork for exploring the relationship between outcome and intention, the relevance of which is still

integral in understanding the clinical therapeutic value of microdosing (Lea et al., 2020a; Rootman et al., 2021; Hartong and van Emmerik, 2022). The case of a placebo response has been conceived in literature; however, the role of this phenomenon in the microdosing practice has yet to be adequately explored (Polito and Liknaitzky, 2023).

Observational studies further described common dosing schedules employed outside more rigid scientific studies. A common schedule is to dose on one day, followed by a two-day “off” period where no dose is taken. This protocol was initially ascribed to J. Fadiman, where participants follow this regime for an 8-week cycle and a 4-week break before restarting (Fadiman, 2011). Additional protocols were noted, with a common theme of dose personalisation identified: dosing schedules were commonly achieved through trial-and-error runs for participants to identify an optimal dose and schedule.

Benefits were also variable, with improvements in mood, creativity, focus and cognitive performance cited across studies. However, one study noted an impairment in these categories, emphasising the portentous, subjective experiences of psychedelic use (Anderson et al., 2019a). The illegality of psychedelic substances was also a common challenge among users, as well as unwanted physical side effects from incorrect dosing, such as physical

discomfort or anxiety from taking a dose that was too high to be considered sub-hallucinogenic.

Overall, these observational studies were congruous, citing numerous aforementioned benefits with comparatively few challenges.

Grey literature: web searches

Cross-sectional, anecdotal evidence was obtained through the top ten web searches on psilocybin microdosing (Table 4). Two findings were identified as duplicates of studies from database searches, but were incorporated into *Table 4* for the sake of format. Additionally, study design was not included as the information was exclusively narrative.

Table 4: Anecdotal findings (web searches)

Author	Title	Web Page	Findings
T. Anderson; R. Petranker; A. Christopher *et al.* (Anderson et al., 2019a)	Psychedelic microdosing benefits and challenges: An empirical codebook	*Duplicate: refer to Table 3*	*Duplicate: refer to Table 3*

P. Grinspoon (Peter Grinspoon, 2022)	The popularity of microdosing of psychedelics: What does the science say?	Harvard Health Publishing	Psilocybin microdose: ~ 0.3 g mushroom; mushroom potency varies; identify correct mushroom to avoid poisoning; recognised as safe in low doses (used by indigenous peoples for centuries) No conclusion on microdosing efficacy; consultation with doctor recommended before attempting practice
S. Radcliffe (Radcliffe, 2022)	Microdosing Psilocybin Mushrooms May Improve Mental Health and Mood	Healthline	Discussion of results from various sources: observational study published in nature; Global Drug survey; psychomotor benefits from psilocybin microdosing Research results mostly observational; expectancy may contribute to outcome; possible cardiac damage from long-term psilocybin use (valve damage/cardiac valvopathy) to be

			investigated in microdosing; more research recommended
No Author (PABCounseling, n.d.)	Microdosing Psilocybin aka Magic Mushrooms	PABCounseing (Pediatric and Adult Behavioral Counseling)	Psilocybin: compound from "magic mushrooms"; prodrug of psilocin; indole alkaloid similar to serotonin structure; a classic psychedelic; alters sensory experiences; increases empathy; distorts time; negative effects such as increased heart rate & paranoia Microdosing psilocybin: **benefits** include increased creativity/energy/focus/mood/sense, decreased agitation, relieved PMDD/anxiety/depression symptoms, treating addiction Dose: 0.25 - 0.50 g dry mushrooms OR 2.5 - 0.5mg synthesised psilocybin capsule Recommendations: low dose for first time then increase as

			necessary; administer orally at start of day for 3-4 consecutive days; find appropriate help for dosing & treatment plans; be careful about daily use to avoid building tolerance quickly Psilocybin overdose not common, but may cause food poisoning/accelerate nervous system/negatively affect liver
E. Glover (Glover, 2022)	So you want to start microdosing mushrooms?	Dazed	Discussion of various study outcomes & psilocybin safety Microdosing psilocybin: 0.1 - 0.9 g; powder/whole/boiled into tea; common regime to dose every other day for 2 weeks followed by week off; recommend taking breaks to monitor effect; don't take with alcohol; rather buy dry mushrooms from trusted source than picking

			Inform someone if practice is undertaken; meditate/calm breathing if discomfort occurs
D. G. Smith (Smith, 2022)	More People Are Microdosing for Mental Health. But Does It Work?	New York Times	Microdosing testimony; anecdotal evidence from literature & study limitations (eg, small sample size) Psilocybin: mushroom potency varies - trial & error for dosing
F. Cavanna; S. Muller; L. A. de la Fuente (Cavanna et al., 2022)	Microdosing with psilocybin mushrooms: a double-blind placebo-controlled study	*Duplicate: refer to Table 2*	*Duplicate: refer to Table 2*
J. C. Hu (Hu, 2023)	Microdosing psychedelics has benefits, users say. Science isn't convinced.	The Washington Post	Report microdosing back to 1500s; western world microdosing since 1960's Microdosing testimony; anecdotal evidence from literature

S. LaMotte (LaMotte, 2023)	How psilocybin, the psychedelic in mushrooms, may rewire the brain to ease depression, anxiety and more	CNN Health	Discuss psilocybin mushroom benefits & long-term effects Psilocybin microdose: ~0.1 - 0.3 g dry mushroom Stacking: mushroom microdose + substances to boost benefits: "Stamets Stack": niacin (vit B3) + Lion's mane Positive feedback from online surveys (via P. Stamets website/app "Microdose Study"): register & self-report on microdosing No research conclusion on efficacy/benefit
No Author Medically reviewed by: Dr. Sanjai Thankachen (Thankachen, 2023)	Microdosing Psilocybin: The Pros, Cons, and Unknowns	Healthy Life Recovery	Psilocybin: hallucinogen found in certain mushroom spp; mushroom potency varies; activates 5-HT receptors in prefrontal cortex; ~ 30 mins for onset; psilocybin content ~10x higher in dry vs fresh mushroom; possible risk from long-term use to be determined

			(psilocybin metabolised by liver into psilocin - binds to heart 5-HT receptors) Microdosing psilocybin: ~ 5 - 10% of regular dose; effects not extensively researched to date; extrapolation of higher dose evidence; anecdotal evidence discussed (improved mental health, focus, enhanced brain functioning, quitting other habits) No conclusion if psilocybin microdosing safe & effective

Five of the 10 websites pertained exclusively to microdosing with psilocybin. The availability of open-access, peer-reviewed literature provided credible groundwork to the information synthesised on websites. The majority of websites made reference to and/or discussed scientific studies, as well as prominent researchers within the psychedelic field including Nutt, Fadiman and Stamets. Information discussed on websites were congruous and reflected the current evidence from scientific studies in that no conclusions were made on the efficacy

of microdosing as a practice. Instead, these websites provided conversational information regarding psychedelics, such as their definition, their effects, on-going research investigating their uses as well as the definition and nature of microdosing as a practice.

Regarding safety, two articles discussed the potential long-term effects of psilocybin on heart function (PABCounseling, n.d.; Thankachen, 2023).

Instructions on how to microdose psilocybin were broad, providing dose definitions as well as examples of administration forms (tea, capsules, etc). *CNN health* described the practice of “stacking”, in which a few other substances are administered in combination with psilocybin to add to the benefit of the mushrooms (LaMotte, 2023). *CNN health* referenced a large-scale, online microdosing study entitled “Microdose.me” where participants contributed towards an extensively large pool of anecdotal evidence. The results of this study have been included in Table 3 (Rootman et al., 2021).

Discussion

This review set out to investigate the current peer-reviewed and grey literature pertaining to microdosing practices with psilocybin. Studies ranging from non-clinical to qualitative surveys/questionnaires to double-blind placebo-controlled have been published predominantly in the last 5 years. It is apparent that the science of microdosing is still emerging, and that psilocybin-exclusive microdosing studies are comparatively few. Thus, it could be considered inevitable that disparities exist.

Neither the definition nor the precise dose of a microdose are standardised. Microdosing is loosely defined across literature with common, underlying concepts that distinguish the practice as the administration of sub-threshold doses of hallucinogenic substances such as psilocybin to obtain benefit without experiencing the cognitive and perceptual distortion associated with higher hallucinogenic doses. A common dose approximation is between one tenth and one twentieth of an acute dose. However, due to the natural range in potency in psilocybin-producing organisms, as well as the flexible nature of self-administration, defining and standardising a microdose in a clinical setting is not straightforward. Psilocybin microdoses are administered as measures of dried mushrooms in some studies, ranging between 0.1 g to 1 g, while some studies administer doses as a proportion of pure psilocybin per kilogram (e.g., 0.1 mg/kg). Studies of observational data from participants with established microdosing

regimes commonly define a dose *range* across participants instead of a solitary dose, emphasising the point that one size does not fit all.

The effects of set and setting on psychedelic experiences and outcomes have been extensively investigated in acute dosing, further highlighting the subjective effects psilocybin has on individuals. However, these elements of subjectivity could be a limitation in microdosing studies where doses are standardised rather than optimised. Standardised doses may not produce desired outcomes in participants if the dose is not tailored to their specific psychology and physiology.

Set and setting, inactive placebo controls as well as previous psychedelic exposure are possible contributing factors relating to the participant unblinding observed across several studies. Substances used as placebo included non-psychoactive mushroom, microcrystalline cellulose, saline or were not disclosed (Schindler et al., 2022; Horsley et al., 2018; Marschall et al., 2022).

The integrity of participant blinding in placebo-controlled studies has been a confounding variable in some results, prompting queries about the relationship between motive, expectation and outcome. Additionally, the extensively observed unblinding supports the current query regarding the use of the term “sub-perceptual” as opposed to “sub-hallucinogenic”: perhaps doses are small enough

to not result in a hallucinogenic effect, but still bring about a tangible difference by comparison to baseline.

Most observational evidence investigating therapeutic outcome was positive, providing more beneficial outcomes, such as improvements in mood, creativity, focus and performance, than challenging ones, such as physical discomfort, paranoia and issues related to the illegality of psychedelic substances (e.g., procurement). However, the scientific value of the descriptive and observational nature of certain studies, such as case reports, is comparatively lower than the more rigorous design of double-blind, placebo-controlled trials. As such, a large question surrounds the nature of the perceived benefits reported in observational studies: some studies provided findings in support of a direct therapeutic benefit, while others alluded to the possibility that effects are owed to a placebo response. However, the extent of placebo involvement in microdosing studies has yet to be determined presently, with several recent aspects postulated for the consideration of further research (Polito and Liknaitzky, 2023).

Furthermore, while the therapeutic effect of psilocybin on the serotonergic system has been extensively researched, its mechanism of action in microdosing outcomes is not yet well-understood. Current research on the biological biomarkers involved in the mechanism of action of acute psilocybin doses, such as cytokines and brain-derived neurotrophic factor (BDNF), are currently under

investigation (Mason et al., 2023; Du et al., 2023). However, the involvement of several psychological biomarkers, such as those relating to the cognitive subjectivity of both acute and microdose psilocybin experiences, hinders conclusions on the topic (Carhart-Harris et al., 2017). Thus, the relationship between expectation and outcome has yet to be agreed upon in microdosing studies.

It is possible that the variation in outcomes may reflect differences in frequency and dose, some of which may be at the margins of those required to induce a "therapeutic" effect, which in turn strongly suggests that the efficacy spectrum of psilocybin exhibits a strong dose response relationship. Dose response curves, including cumulative dose effects of multiple small doses, can easily be charted using functional magnetic resonance imaging (fMRI) and biological markers. The threshold dose for these effects is unknown and is therefore the thrust of future research. Further objective psilocybin studies utilising fMRI, such as the study conducted by Murphy *et al.,* would be a valuable asset for these investigations (Murphy et al., 2021).

It could be argued that providing those who are willing and proactive in their mental well-being with a self-management tool that offers therapeutic value to any degree, is not a fallacy. This is especially pertinent within the context that many microdosers considered the practice to be a deliberate choice towards well-

being and not recreational drug use. For example, a study found microdosers possessing a scientifically professional attitude towards the practice (Ryan et al., 2023). Common motivations for the practice centred around themes of self-improvement and self-management. Some studies reported the practice as a "catalyst" for participants who already possessed willingness for self-improvement, while many others reported participants who microdose as an adjunct to standard therapeutics for various psychiatric morbidities (Kinderlehrer, 2023). Additionally, the practice is often regarded as an act of well-being by users and not specifically a curative agent for any particular disease. Thus, it is clear that participant selection is pivotal to understanding the underlying therapeutic mechanism of psilocybin microdosing. In context, this could potentially offer insight into the growing popularity of microdosing strategies among the general public, as these practices do not require extensive clinical supervision and are easily adopted into routines.

The majority of studies investigating the perceived benefits and effects of microdosing have been self-reporting, survey-based. These studies have provided substantial observational evidence. However, various limitations exist, such as sampling bias, lack of experimental control, lack of placebo control groups and small sample sizes, among others (Lyons, 2022; Lyes et al., 2023; Schindler et al., 2022). A range of perceived benefits have been reported from

these studies including mood/mental health improvement, cognitive enhancement pain management, creativity enhancement and social enhancement; conversely, adverse effects have also been reported, commonly relating to anxiety or physical effects such as unwanted stimulation and unexpectedly high (psychedelic) doses (Johnstad, 2018; Anderson et al., 2019a; Hartogsohn and Petranker, 2022). The safety of psilocybin microdosing has not been explicitly explored, although psilocybin at hallucinogenic doses has, demonstrating its overall safety (Ballenger, 2008; Gukasyan et al., 2022; Straumann et al., 2024). However, further investigation is warranted on the mechanisms of unwanted effects in microdosing practices and how to mitigate them. Recent literature has investigated the potential risk that microdosing practices pose on cardiac function, focussing on the partial agonism of the 5HT-2_B receptor, and its role in drug-induced cardiac fibrosis (Rouaud et al., 2024), valvular heart disease (Tagen et al., 2023) and QT-prolongation (Becker et al., 2022). Articles identified via web searches aligned with this literature - some mentioned the possible unwanted side effects of long-term psilocybin use on cardiac function. It is important to prioritise this safety research to best advise clinical practice.

In contrast, non-clinical and clinical trial assessments were few. By comparison to established observational evidence, animal studies have yet to produce results

that expand upon or explain these findings. Various limitations have been reported with rodent models in the investigation of the efficacy of psilocybin microdosing, further demonstrating that establishing and refining functional and validated rodent models for common microdosing indications are necessary (Hales et al., 2014). Refined animal models may inform downstream clinical study designs. Animal models may also contribute to the growing understanding of the molecular action, biological rationale, dose-response and toxicity ranges of psychedelic substances such as psilocybin (Murnane, 2018). As such, it is recommended not to neglect non-clinical models in the face of growing clinical-based research.

While a substantial amount of observational-based evidence is available, the need for double-blind, placebo-controlled studies to substantiate the findings of these studies is also necessary. Thorough consideration of placebo unblinding is integral to the progression of this type of study design.

The demographics of the participants included in microdosing studies were predominantly Caucasian males and people from the USA. Speculation on these statistics cannot be accurately deductive, however, this highlights the need for more diverse sample populations. Due to many studies having recruited participants who have either a history of or interest in microdosing, sample bias could potentially affect results.

There is an overall lack of psilocybin-exclusive microdosing studies. Although it was found that microdosing practices may include the concurrent use of LSD, MDMA and psilocybin, there is an absence of studies that enquire about polydrug use in the context of microdosing. This is important as potential drug-drug interactions with various psychiatric and other treatments may cause unwanted and potentially serious effects, such as the increased potential for serotonin syndrome (Sarparast et al., 2022). As psilocybin is a commonly used psychedelic in microdosing practices, it is pertinent that future studies specifically interrogate this unregulated practice. This would further contribute to the pool of available information that the general public utilises when considering or adopting a microdosing routine.

There is some overlap with the systematic review by Polito and Liknaitzky (2022) who performed a risk of bias analysis on their 44 studies of psilocybin, LSD, DMT and ibogaine microdosing, placing emphasis on cognitive and neurological changes that occur in altered states of consciousness with categories including mood and mental health, wellbeing and attitude, cognition and creativity, personality, changes in conscious state, and neurobiology and physiology. The systematic review included qualitative studies (interviews, free response questionnaires, and analyses of internet forums or videos), retrospective survey studies (about past microdosing experiences), prospective studies (microdosing

at multiple time points), and laboratory studies (the acute effects of microdoses administered in a controlled environment). There was good laboratory evidence for microdosing in terms of acute pain perception, time perception, and subjective awareness. Although these laboratory studies offered a higher degree of experimental control and therefore carried a lower risk of bias, they might not fully capture how the effects of microdosing develop over time. The authors also noted that no clinical trials had been conducted on the efficacy of microdosing for clinical indications such as depression. Although, two of the clinical trials included here investigated the therapeutic effects of psilocybin microdosing on obsessive compulsive disorder and cluster headaches, this research gap needs to be addressed. Several universities (University of Toronto, Maastricht University, Imperial College London, Macquarie University) are currently investigating the effects of microdosing psilocybin on mental health outcomes, including on moderate depression, but these studies are not necessarily randomised controlled clinical trials.

Several research gaps were identified in this semi-structured review:

*Randomised, placebo-controlled trials***:** The majority of studies are qualitative, descriptive reports. Placebo-controlled studies are available; however, several considerations should be addressed before proceeding with further studies (see below).

Dose range: There is a lack of standardisation in dosing due to the nature of varying mushroom potencies, as well as flexible dosing for personalised regimes. Investigating these real world, flexible doses in randomised, placebo-controlled studies would help establish which doses are sub-therapeutic, effective or out of range. Psilocybin dose-response curves based on subjective clinical effects and objective biological markers such as fMRI changes would add significantly to current microdosing evidence.

Psychological and personality tests: Incorporating rigorous psychological- and personality-based assessments when recruiting and selecting participants to identify the archetypical person who microdoses could potentially aid in the prevention of unblinding. It would also further the framework of understanding the motivations and indications for microdosing.

*Active placebo***:** Many studies report unblinding of placebo and active arms. Refining an active placebo could help prevent unblinding. Comparison of different sub-hallucinogenic doses of psilocybin could potentially mitigate these challenges.

*Population pool***:** Incorporating psychedelic-naïve populations in studies would be valuable in sample selection. Additionally, ensuring a more diverse demographic would generate results that are more readily translatable to different populations.

Psilocybin-exclusive studies: Studies exclusively investigating the safety, efficacy and indications of psilocybin microdosing are still emerging. Currently, a large part of information on microdosing with psilocybin exists in studies concerning microdosing as an over-arching concept. Much like studies specifically investigating the acute effects of psilocybin, investigating the effects of psilocybin microdosing exclusively would make information such as psilocybin-specific biomarkers, possible unwanted effects on cardiac function as well as drug-drug interactions with common psychiatric medications more accessible.

Refinement of animal models: Despite the growing body of evidence obtained through clinical studies, it is of interest to refine pre-clinical models.

Limitations

The cross-sectional scope of information on Google websites is noted as an incomplete scope of all web-based information on microdosing. The rationale of including these websites has been previously discussed. However, conducting a complete web-based review of online information is outside the scope of this review. Future research should consider the potential of web-based information in microdosing research.

There were insufficient and inadequate primary data to conduct a quantitative summary and subsequent meta-analysis.

Conclusion

Research on psilocybin microdosing is still relatively new compared to acute dosing, although substantial observational evidence supports its practice. Numerous research gaps were identified, including the need for more randomised, placebo-controlled trials; the investigation of dose ranges as opposed to single doses; conducting psychological and personality testing on trial participants; making use of an active placebo; incorporating a more diverse population pool, the need for more psilocybin-exclusive studies and the refinement of animal models.

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The authors declare no conflict of interest.

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