**Macrodosing to Microdosing with Psychedelics:**

**Clinical, Social, and Cultural Perspectives**

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**Abstract:**

To date, the clinical and scientific literature has best documented the effects of classical psychedelics, such as lysergic acid diethylamide (LSD), psilocybin, and dimethyltryptamine (DMT), in typical doses most often associated with macrodosing.  More recently, however, microdosing with psychedelics has emerged as a social trend and nascent therapeutic intervention.  This variation in psychedelic practice refers to repeat, intermittent ingestion of less-than-macrodose amounts that do not cause the effects associated with full-blown “trips”. Microdosing paves the road to incorporating psychedelic drugs into a daily routine while maintaining, or even improving, cognitive and mental function.  Unlike macrodosing with psychedelics, the influence of microdosing remains mostly unexplored.  And yet, despite the paucity of formal studies, many informal accounts propose that microdosing plays an important role as both a therapeutic intervention (e.g., in mental disorders) and enhancement tool (e.g., recreationally--to boost creativity, improve cognition, and drive personal growth).  In response to this relatively new practice, here we provide an integrative synthesis of the clinical, social, and cultural dimensions of microdosing.  We describe some of the overarching context that explains why this practice is increasingly in vogue, unpack potential benefits and risks, and comment on some future socio-cultural implications.  This paper juxtaposes the effects macro- and micro-doses have on behavior and psychopathology because of their unique dosage features and settings. Finally, our discussion outlines the merits and drawbacks associated with this recent practice.

keywords: microdosing, classical psychedelics, macrodose, LSD, psilocybin.

**Introduction**

Punctuated by a checkered history, psychedelic substances propel mind-altering experiences that may have both therapeutic and recreational value (Nichols, 2016; Vollenweider, Vollenweider-Scherpenhuyzen, Bäbler, Vogel, & Hell, 1998).  Classical psychedelics, such as lysergic acid diethylamide (LSD), psilocybin, dimethyltryptamine (DMT), mainly work through 5-HT2A receptor agonism, inducing altered states of consciousness by affecting perception, mood, and thought (Preller & Vollenweider, 2016; Vollenweider et al., 1998).  Here is a typical description that captures the experience of ingesting a full dose classical psychedelic:

“Without causing physical addiction, craving, major physiological disturbances, delirium, disorientation, or amnesia, [it] more or less reliably produces thought, mood, and perceptual changes otherwise rarely experienced except in dreams, contemplative and religious exaltation, flashes of vivid involuntary memory, and acute psychosis” (Grinspoon & Bakalar, 1981, p. 9).

In line with the modern cultural and scientific interest in psychedelics, more recently, the practice of microdosing, with a typical protocol of ingesting one tenth to one twentieth of a regular dose every three-to-four days, has emerged (Fadiman, 2011).  It has become a popular practice, with hundreds of individuals reporting benefits in creativity and productivity, and paving the road to “microdosing” becoming interchangeable with “nootropics” (Machek, 2019), “smart drugs” (d'Angelo, Savulich, & Sahakian, 2017), or “mental tonics” (Pollan, 2019, p. 304).

In this comprehensive review, we examine research findings with classical psychedelics (e.g., LSD, psilocybin, DMT) in high- and low- doses, explore commonalities and differences in between two cases, contextualize the recent practice of microdosing, and discuss the clinical, social, and cultural implications of this new practice.

**Macrodoses**

Plants and plant-based derivatives possessing mind-altering effects have been a part of ritualistic settings for centuries (Schultes, 1969).  Despite their rich history and documented use by indigenous healers in different cultures, psychedelics did not appear in modern medicine until the isolation of mescaline from the peyote cactus by Arthur Heffter in 1896 (Heffter, 1896) and the synthesis of LSD from ergot fungus by Albert Hofmann in 1938 (Hofmann, 1979).  Thereafter, Hofmann accidentally stumbled upon the psychoactive properties of LSD, and since then, psychedelics have become a focus of interest for their therapeutic potential in clinical and research settings.  Several clinical trials have been subsequently published showing promising results, especially in the treatment of alcohol dependence (Bowen, Soskin, & Chotlos, 1970; Hollister, Shelton, & Krieger, 1969; Kurland, 1985; Tomsovic & Edwards, 1970), opioid dependence (Savage & McCabe, 1973), end-of-life distress in cancer patients (Grof, Goodman, Richards, & Kurland, 1973; Kurland, 1985; Kurland, Grof, Pahnke, & Goodman, 1972), and pain (E. Kast, 1967; E. C. Kast, 1964; E. C. Kast & Collins, 1964).  However, scholars have subsequently criticized the majority of these trials as methodologically weak and suboptimal (e.g., for not having control groups or blinding) (Rucker, Iliff, & Nutt, 2018).  In addition, a mixture of social trends, confusion, fear, and political tension (e.g., many young Americans who used psychedelics recreationally dodged the Vietnam draft) complicated the picture (Nutt, King, & Nichols, 2013).  Simultaneously, public opinion concerning psychedelics responded to “media sensationalism, lack of information, and cultural biases, rather than evidence-based harm assessments” (Johansen & Krebs, 2015).  So, pitted against a backdrop of problematic recreational use and the zeitgeist against a growing counter-culture (Dyck, 2005), in the 1960s LSD and psilocybin made their way into the “Schedule I” category of drugs, deemed by the U.S. government to have a high potential for abuse without an accepted medical benefit.

However, in retrospect, conventional clinical wisdom has confirmed that LSD and psilocybin rank as some of the least harmful drugs of abuse, certainly less than alcohol and tobacco (Nutt, King, & Phillips, 2010).  Moreover, classical psychedelics are seen as an anomaly among illicit drugs because they have extremely low potential of abuse, as they do not cause compulsive drug seeking, and are not associated with withdrawal syndrome (Johnson, Richards, & Griffiths, 2008; O’Brien, 2001).  In contrast to other illicit drugs of abuse, population studies have found no association between psychedelic use and negative mental health outcomes (Krebs & Johansen, 2013).  Instead,a lifetime of use of psychedelics is found to be correlated with lower levels of psychological distress (Hendricks, Thorne, Clark, Coombs, & Johnson, 2015), reduced likelihood of criminal behavior (Hendricks, Clark, Johnson, Fontaine, & Cropsey, 2014; Hendricks et al., 2018), and reduced intimate partner violence (Thiessen, Walsh, Bird, & Lafrance, 2018).

After a lacuna in the field of psychedelic research that lasted from the 1970s to the 1990s, we are now witnessing an incipient, “psychedelic renaissance” (Sessa, 2012).  In this second coming of psychedelic research, contemporary studies have examined the clinical benefits of psychedelics in the treatment of depression (R. Carhart-Harris et al., 2018; Carhart-Harris et al., 2016; Osório et al., 2015; Palhano-Fontes et al., 2019; Sanches et al., 2016), end-of-life distress with terminally-ill patients (Gasser et al., 2014; Griffiths et al., 2016; Grob et al., 2011), alcohol dependence (Bogenschutz et al., 2015), tobacco dependence (Johnson, Garcia-Romeu, Cosimano, & Griffiths, 2014), obsessive-compulsive disorder (Moreno, Wiegand, Taitano, & Delgado, 2006).

**Microdoses**

Unlike the vast literature addressing macrodoses, or the nascent effort to study megadoses (Brown et al., 2017) of psychedelics, the effects of low doses remain underexplored.  However, anthropological accounts mention the use of psychedelic substances in low doses for a variety of therapeutic effects (e.g., to increase libido, to reduce appetite, to increase courage, and to treat some inflammatory and infectious disorders) (Prioreschi, 1991).  Reported accounts of use among the Aztecs document their consumption of small amounts of psilocybin-containing mushrooms, ingested over several consecutive days, for rheumatic pain and fever (Schultes, 1940), as well as to increase visual acuity for hunting (McKenna, 1999).

Albert Hofmann mentioned the use of very low doses of LSD as an antidepressant or psychostimulant (Horowitz, 1976).  However, there was no formal research on microdosing prior to the prohibition of psychedelics in 1967, and the practice didn’t become popular until after the publication of James Fadiman’s book, The Psychedelic Explorer’s Guide, which was the first to describe microdosing with psychedelics in detail (Fadiman, 2011).  Fadiman outlined the benefits of microdosing, 3-day cycle, and guidelines for dosing.  This book contains dosing scripts, including anecdotal case reports, mostly emphasizing positive improvements.  Following Fadiman’s book, many stories on microdosing appeared in the popular media, with a particular focus on people working in the technology sector (Dean, 2017; Glatter, 2015).  Among the benefits of microdosing, individuals reported improvement in creativity and productivity. Moreover, they preferred microdosing to psychostimulants as a cognitive enhancer (d'Angelo et al., 2017). Non-scientific literature and practices of microdosing have grown in proportion to scientific attention and inquiry into psychedelic use in moderate to high doses.

Different from its use and definition in clinical pharmacology (Tewari & Mukherjee, 2010), in psychedelic literature microdose defines a dose range that does not cause marked perceptual alterations (such as hallucinations), so it is labeled sub-perceptual, sub-hallucinogenic, and sub-psychoactive doses.  LSD and psilocybin comprise the most common substances used in microdosing when following a schedule-protocol of intermittent ingestion, spaced across a week (Anderson, Petranker, Rosenbaum, et al., 2019; Hutten, Mason, Dolder, & Kuypers, 2019).  Intermittency stems from concerns about tolerance, which some studies report as occurring within three days (Cholden, Kurland, & Savage, 1955; Isbell, Belleville, Fraser, Wikler, & Logan, 1956).  In the case of DMT, however, tolerance seems irrelevant, probably because of its shorter half-life and drug metabolism (Galvão et al., 2018; Schindler, Wallace, Sloshower, & D’Souza, 2018).  Another reason to microdose every few days, rather than daily, speaks to the persisting effects of psychedelics (R. Carhart-Harris et al., 2018; Garcia-Romeu, R Griffiths, & W Johnson, 2014; Griffiths et al., 2011; Griffiths, Richards, Johnson, McCann, & Jesse, 2008; Griffiths, Richards, McCann, & Jesse, 2006).  Accounts in the popular and trade press mention that the beneficial effects of microdosing would carry over for one or two days after ingestion (Fadiman, 2011; Waldman, 2018).  However, in an online survey, microdosers reported positive effects for only the dosing day (Polito & Stevenson, 2019).

Preclinical studies with microdosing report a mixed bag of effects, from anxiogenic (Horsley, Páleníček, Kolin, & Valeš, 2018) to anxiolytic and antidepressant (Cameron, Benson, DeFelice, Fiehn, & Olson, 2019; Sakloth et al., 2019).  Studies with rats reveal that males gain weight whereas females do not.  Female rats display a decrease in dendritic spine density whereas males do not (Cameron et al., 2019).  A preclinical study with 52 male rats found no evidence of abuse potential of repeated treatment with low doses of LSD (Sakloth et al., 2019).  However, issues related to interspecies scaling make such data difficult to generalize (Kuypers et al., 2019).

Online surveys and observational studies on microdosing reported improved creativity, mood, and cognition (Johnstad, 2018; Polito & Stevenson, 2019; Prochazkova et al., 2018), increased sociability (Webb, Copes, & Hendricks, 2019), lower dysfunctional attitudes, lower negative emotionality, higher wisdom, and open-mindedness (Anderson, Petranker, Christopher, et al., 2019).   However, the first double-blind, placebo-controlled trial of microdosing found no significant changes in perception, concentration, and consciousness (Yanakieva et al., 2019).  In an online observational study, reduction in depression and stress levels, lower levels of distractibility, increased absorption, and increased neuroticism have been reported at the sixth week follow-up evaluation of microdosing (Polito & Stevenson, 2019).  In a web-based prospective survey, positive expectations indexed improvements in mental health (Kaertner et al., 2021). While the majority of online studies report beneficial effects, a few studies investigated downsides and challenges regarding microdosing (Anderson, Petranker, Christopher, et al., 2019; Hutten et al., 2019; Polito & Stevenson, 2019).  The most common negative responses were problems with dosing, physiological discomfort (e.g., temperature dysregulation, insomnia, reduced appetite, headaches), increased anxiety, and illegality of obtaining psychedelics.

**Discussion**

Recent systematic reviews have reported that, when administered in supportive and controlled settings, classical psychedelics in macrodoses bring about immediate, substantial, and sustained outcomes, even after a single dose (Aday, Mitzkovitz, Bloesch, Davoli, & Davis, 2020; Bouso, dos Santos, Alcázar-Córcoles, & Hallak, 2018; Dos Santos, Bouso, Alcázar-Córcoles, & Hallak, 2018; Muttoni, Ardissino, & John, 2019; Reiche et al., 2018).  After careful screening of individuals to control for the risk of relevant psychiatric and medical conditions, clinical interventions ensure a good tolerability and safety profile, largely devoid of persistent side effects.  Research shows promising results for the treatment of depression, anxiety related to terminal illnesses, and addiction.  In addition, psychedelics have recently been dubbed “psychoplastogens”, acknowledging their role in neural plasticity and thereby intimating, for example, their potential in treating neurodegenerative disorders (Ly et al., 2018; D. E. Olson, 2018).  In addition, some scholars have claimed that these substances possess anti-inflammatory properties and may be good candidates for treating such disorders, perhaps in lieu of steroids (Flanagan & Nichols, 2018).  Even more, as agents propelling an altered state of consciousness, psychedelics have been proposed as treatment options for disorders of consciousness (Scott & Carhart-Harris, 2019).  These promising directions, largely motivated by the rekindling of psychedelic research, have recently motivated the Food and Drug Administration (FDA) to grant psilocybin “breakthrough therapy” status for treatment-resistant depression.  Altogether, these steps seem to herald the first attempts to include psychedelics in mainstream clinical medicine.

According to anecdotal reports and preliminary evidence, microdosing with psychedelics has potential as a psychostimulant or cognitive enhancer, antidepressant, and psychoplastogen, with its own clinical benefits (Kuypers et al., 2019).  For example, microdosing can offer a treatment option for attention deficit hyperactivity disorder, depression, and neurodegenerative disorders.  However, these relative merits come with related risks, as in the case of psychostimulants, microdosing may trigger potential for psychological abuse by enhancing mood, energy, and cognition (Maier & Schaub, 2015).  In addition, frequent and chronic exposure to psychedelics may lead to cardiac valvulopathy by repeated activation of the 5-HT2B receptor (Elangbam et al., 2008).

The illegality of psychedelics increases health risks because thousands of users obtain their substances from unknown sources or prepare their materials by themselves.  Some countries have acknowledged the risks and changed their laws to mitigate them.  Portugal, for example, decriminalized illicit drugs as a harm-reduction approach in 2001; thereafter, it reaped a decrease in problematic drug use and drug-related harms (Hughes & Stevens, 2007).

Due to its legal and regulatory status, research with psychedelics faces many challenges (Kuypers et al., 2019).  Because of their legal status in many countries, research with psychedelics often relies on self-report and online surveys.  On the one hand, this method offers the advantage of reaching out to many participants in spite of local laws and their legal status.  On the other hand, it poses disadvantages when it comes to representative samples, reliability, and selection bias (Hutten et al., 2019).  Last, but not least, some caveats to research with self-reports and surveys include problems with drug purity, concomitant drug use, precise dosing, and screening for psychiatric and medical conditions.  And yet, microdosing is an advantageous focus for such research, not requiring as much clinical oversight as macrodosing (Anderson, Petranker, Rosenbaum, et al., 2019).  Also, future research might benefit from comparing data from psychedelic-naive participants with that of experienced individuals, and microdosing offers a safer and gentler entry point by largely bypassing the stigma and fear around these substances, especially for those new to them.  Given that cultural factors fuel both the psychedelic experience (Bunce, 1979) and placebo effects (Moerman & Jonas, 2002), future research may benefit from conducting cross-cultural studies between places where psychedelics are illegal and stigmatized and those where they are legal and embraced (R. L. Carhart-Harris et al., 2018).

In fact, historical records, phenomenological reports, recreational accounts, and scientific experiments with psychedelics show that their effects seem context-dependent both in the psychological and environmental sense.  The importance of contextual factors in the psychedelic experience has long been known and utilized by indigenous people and shamans in traditional ceremonies (R. L. Carhart-Harris et al., 2018).  Psychedelic pioneers were interested in the cultural uses of plant medicines, and the term “set and setting” in psychedelic experience was introduced by Timothy Leary (Leary, Litwin, & Metzner, 1963).  He defined “set” as pre-existing psychological factors one brings to an experience including personality, psychopathology, preparation, expectation, assumption, and intention; and “setting” as environmental context including physical (e.g., flowers, blankets, songs), social (e.g., shamans, clinicians, group of friends), and cultural elements (e.g., public opinion, media representation, legal and regulatory stance) in which the experience occurs.  Additionally, cultural discourse differs between psychedelic substances (Dyck, 2018). For example, whereas psilocybin and ayahuasca have a long history as respected “plant teachers” for centuries, LSD is merely a laboratory product of modern science with a much shorter history of use. As the cultural climate changes, so will the effects (Becker, 1967).

Psychedelic-assisted psychotherapy has benefited from and improvised on this awareness (Fadiman, 2011).  For example, in one study, LSD-induced changes in brain dynamics associated with changes in personality traits were observed only under conditions including listening to music (Lebedev et al., 2016). On the other hand, when contextual factors are neglected, psychedelic experience has been found to be clinically ineffective (R. L. Carhart-Harris et al., 2018). When the context is manipulated in a negative way, as in the military experiments with psychedelics in the 1950s, harm, such as deteriorating in mental states, has been observed (Albarelli, 2009). These damaging results increased the unwarranted stigma and fear around psychedelics for a long time (R. L. Carhart-Harris et al., 2018).

Set and setting theory and placebo response theory are two fields which consider how extra- or non-pharmacological/biological factors related to cognition and meaning modulate and shape the response to a given therapy (Hartogsohn, 2016).  Literature on placebo effects shows that non-pharmacological factors constitute a substantial part of therapeutic effectiveness (Kirsch & Sapirstein, 1999).  For example, in the case of antidepressants, placebos and antidepressants seem clinically comparable for the treatment of mild-to-moderate depression (Kirsch, 2014; Munkholm, Paludan-Müller, & Boesen, 2019).  By some twist of placebo irony, some clinicians know antidepressants may be effective at the sub-therapeutic dose pointing to the placebo component as part of the effective treatment (Furukawa, McGuire, & Barbui, 2002; McCormack, Allan, & Virani, 2011).  The “meaning response” has construed placebo effects as psychological and physiological effects generated by the meaning associated with a treatment; it relates how we understand healing, illness, ritual and symbols of a therapy (Moerman & Jonas, 2002).  Similarly, placebo effects are further conceptualized as contextual healing (Miller & Kaptchuk, 2008).  By the same token, psychedelics have been framed as meaning-response magnifiers, or as hyper-active placebo catalysts, perhaps by amplifying contextual factors and expectations (Hartogsohn, 2016, 2020).  Compared to regular doses with psychedelics, contextual factors (setting) may be less influential in lower doses as in microdosing, however psychological factors such as expectations and beliefs (set) would still play a big role in drug response.  Positivity bias refers to an effect among individuals with extensive psychedelic experience who appear partial toward microdosing and praise its benefits (Anderson, Petranker, Rosenbaum, et al., 2019; Kaertner et al., 2021).  Moreover, positive reports and media headlines may shape and amplify response expectancies associated with microdosing. These social, situational, and cultural factors shape and drive subjective drug effects (Becker, 1967).  As a result, some individuals may be predisposed to experiencing what they expect, what they believe will follow, and what other people around them seem to experience (J. A. Olson, Suissa-Rocheleau, Lifshitz, Raz, & Veissière, 2020).

Because the effects of a microdose can be minimal, subtle, and ambiguous, microdosers may interpret small changes as being in line with their expectations (Polito & Stevenson, 2019).  In this regard, very small microdoses may pass as placebos, but how low a dose may constitute a placebo remains unclear.  Although the dose that constitutes a microdose remains challenging to determine and operationalize, the nosology calls for amounts that range from infinitesimal but non-homeopathic to about one-tenth of a macrodose.  The jury is still out on whether users should subjectively detect a microdose for its beneficial effects.  However, detectability raises important questions concerning the role of other components (e.g., expectation, conditioning, and placebo responses and effects) within the microdosing context.  Future studies with microdoses would likely provide a better scientific understanding about contextual factors and placebo response by resolving practical (e.g., problems with blinding), and ethical (providing a sub-optimal context) challenges with psychedelic research.

However, either in high or low doses, working with psychedelics involves a number of risks and ethical concerns (Sloshower, 2018).  First, integrating indigenous plants and practices into mainstream medicine carries the risk of cultural appropriation and commercialization of indigenous knowledge by Westerners.  It may appear disrespectful to neglect ritualistic and sacred elements of psychedelic experience. From an indigenous perspective, the use of psychedelic plants in Western medicine continues a history of colonization, bioprospecting, and extraction of pristine cultural heritage, without consent (Gerber et al., 2021). Second, there are ethical medical concerns, such as the principle of “do no harm.”  While classical psychedelics are considered physiologically safe, there are still psychological risks such as acute psychological distress and prolonged psychosis in high doses, especially for patients with pre-existing psychological problems (Johnson et al., 2008). Even if rarely, acute psychological distress and delusions can lead to dangerous behavior to the self and others in unsupervised conditions (Strassman, 1984). Cultural bias, the resulting stigmatization, and legal problems also pose risks to psychological health.  In addition, microdosing for cognitive enhancement raises ethical concerns regarding equality. Microdosing could create positional benefits and increase social competition. On the other hand, it supports self improvement and determination (Colzato, 2018). Lastly, as researchers learned in the past, integrating psychedelics into mainstream psychiatry requires a social responsibility to avoid further prohibition or criminalization of their use.  Currently, and following attitudes toward cannabis, public opinion is beginning to change, with some U.S. locales and communities creating the necessary climate to decriminalize the use of psychedelics (e.g., Denver, CO; Oakland and Berkeley, CA).  In this regard, legal change may catalyze science, and vice versa.

**Table 1: Macrodosing vs. Microdosing**

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
|   | Macrodosing |   | Microdosing |   |
|   | Advantages | Disadvantages | Advantages | Disadvantages |
| Clinical & Research | \*Promise for treatment of depression, substance use disorders, and end-of-life related distress  \*Limited dependence potential\*Long-lasting benefits with a few drug sessions  | \*Regulatory status \*Challenging experiences – “bad trips” \*Concerns about risk of psychosis \*Require long clinical oversight \*Difficult to blind | \*Promise for the treatment of ADHD and depression  \* No robust perceptual disturbances \*Less intense experiences: no “bad trips” \*Less need for clinical oversight \*Easy blinding    | \*Regulatory status \*Unknown risks associated with chronic and repeated use \*Potential for abuse (perhaps similar to psychostimulants) \* Small, subtle effects, too difficult to detect \*Benefits based mostly on anecdotal reports |
| Recreati-onal | \*Potential for personal growth and well-being.    | \*Illegal\*Fear and anxiety \*Impurity of substance creates uncertainty in dosing \*Concomitant drug use\*Risks related with dangerous behavior in uncontrolled environment  | \*Less stigma and fear \*Fits into daily routine, perhaps even enhance it   | \*Illegal\*Impurity of substance creates uncertainty in dosing \*Potentially offers unfair advantage as a performance enhancer? |

 **Conclusion**

Research with classical psychedelics in typical doses shows promising results for various psychiatric and medical conditions.  Because there is a scarcity of formal studies with large sample sizes and long-term follow up periods, the benefits and risks of microdosing are unclear at this time.  However, abundant informal accounts combined with the results of current early research into psychedelics together suggest that microdosing is likely beneficial both clinically and socially.

  Therefore, more rigorous investigation into the effectiveness and safety of short- and long-term use is the only responsible course of action to take. With the ethical concerns in mind, we call for better studies featuring adequate experimental designs and follow up periods. Such studies promise vital information about the applicability of microdosing, and perhaps even macrodosing, in clinical and recreational settings. Specifically, mood and performance enhancing effects of microdosing should be studied further.  Moreover, microdosing could serve as a gentle entry point for psychedelic research.  In fact, we are optimistic that microdosing is set to become a prominent field of investigation in mental health and behavioral science.

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