Microdosing psychedelics: Too much hype, almost no rigorous research

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

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

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

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

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

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

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

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

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

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References

Austin P (2016) *Everything You Want to Know About Microdosing*. Available at: https://thethirdwave.co (2019) Microdosing mushrooms [Online] (accessed 24 June 2019).

Bogenschutz MP and Ross S (2018) Therapeutic applications of classic hallucinogens. *Curr Top Behav Neurosci* 36: 361–391.

Bogenschutz MP, Forcehimes AA, Pommy JA, et al. (2015) Psilocybin-assisted treatment for alcohol dependence: A proof-of-concept study. *J Psychopharmacol* 29: 289–299.

Carhart-Harris RL, Bolstridge M, Rucker J, et al. (2016) Psilocybin with psychological support for treatment-resistant depression: An open-label feasibility study. *Lancet Psychiatry* 3: 619–627.

Fadiman J (2011) *The Psychedelic Explorer's Guide: Safe, Therapeutic, and Sacred Journeys*. Rochester, VT: Park Street Press.

Gasser P, Holstein D, Michel Y, et al. (2014) Safety and efficacy of lysergic acid diethylamide-assisted psychotherapy for anxiety associated with life-threatening diseases. *J Nerv Ment Dis* 202: 513–520.

Griffiths RR, Johnson MW, Carducci MA, et al. (2016) Psilocybin produces substantial and sustained decrease in depression and anxiety in patients with life-threatening cancer: A randomized double-blind trial. *J Psychopharmacol* 30: 1181–1197.

Grob CS, Danforth AL, Chopra GS, et al. (2011) Pilot study of psilocybin treatment for anxiety in patients with advanced-stage cancer. *Arch Gen Psychiatry* 68: 71–78.

Johnson MW, Garcia-Romeu A, Cosimano MP, et al. (2014) Pilot study of the 5-HT2AR agonist psilocybin in the treatment of tobacco addiction. *J Psychopharmacol* 28: 983–992.

Kitchens S (2018) Microdosing's Micromoment. *New York Magazine*. https://www.thecut.com/2018/05/microdosing-guide-and-explainer.html (accessed 15 January 2019).

Osorio Fde L, Sanches RF, Macedo LR, et al. (2015) Antidepressant effects of a single dose of ayahuasca in patients with recurrent depression: A preliminary report. *Braz J Psychiatry* 37: 13–20.

Prochazkova L, Lippelt DP, Colzato LS, et al. (2018) Exploring the effect of microdosing psychedelics on creativity in an open-label natural setting. *Psychopharmacology (Berl)* 235: 3401–3413.

Ross S and Peselow E (2012) Co-occurring psychotic and addictive disorders: Neurobiology and diagnosis. *Clin Neuropharmacol* 35: 235–243.

Ross S, Bossis A, Guss J, et al. (2016) Rapid and sustained symptom reduction following psilocybin treatment for anxiety and depression in patients with life-threatening cancer: A randomized controlled trial. *J Psychopharmacol* 30: 1165–1180.

Ross S and Bogenschutz M (2017) Hallucinogen-assisted psychotherapy. In: B Sadock, V Sadock and P Ruiz (eds) *Kaplan and Sadock's Comprehensive Textbook of Psychiatry*. 10th ed. Philadelphia, PA: Wolters Kluwer.

www.reddit.com (2019) https://www.reddit.com/r/microdosing/wiki/index (accessed 15 January 2019).

Yanakieva S, Polychroni N, Family N, et al. (2019) The effects of microdose LSD on time perception: A randomized, double-blind, placebo-controlled trial. *Psychopharmacology (Berl)* 236: 1159–1170.