Commentary

James Fadiman and Sophia Korb

As microdoses are being used worldwide, this is a timely article. Prudently, the authors have focused on synthesized psilocybin, as it may soon become more available. As our own research has been entirely anecdotal, and although it includes reports from 51 countries and thousands of individuals, it does not answer any of the questions raised here. What our exploratory findings may have done is help raise the level of interest about the reported negative or positive effects and mechanisms of action. While we have added suggestions and noted a few concerns here, the investigations proposed in the article are all necessary and fundamental.

Early on, it could be important to determine if the same weight of psilocybin in a mushroom with its other alkaloids (found in over 100 mushroom species) has a similar behavioural profile to the synthetic. Equally useful, and perhaps eventually as necessary, would be to replicate the same study with LSD-25 and 1P-LSD. The reason for suggesting these equivalence studies is that of the several hundred thousand people known to have microdosed, less than 1% of them actually used the GMP grade psilocybin. If their experiences differ from those using the synthetic substance, a great deal of otherwise correlative data would need to be put aside.

It seems to us that the worry about cardiac valvulopathy is excessive, given the overall safety profiles of all of the classic psychedelics described in several of Dr. Nutt's publications.

The Fen-Phen experiences of heart valve disease development in the 1980s and 1990s inspired new research in identifying the specific 5-HT receptor subtype involved in drug-induced heart valve disease. In the cases of cardiotoxicity and Fen-Phen, both 5-HTP2A and 5-HTP2B are implicated. In fact, 'norfenfluramine was found to be two orders of magnitude more potent at 5-HT_{2B} and 5-HT_{2C} receptors compared with 5-HT_{2A} receptors' (Hutcheson, 2011). While we have some information about the affinity of LSD towards different receptors, we have little information about how its unique 'crystal structure' may result in different heart health outcomes (Wacker et al., 2017).

Affinity does not tell the whole story. The doses of Fen-Phen used in the 1980s and 1990s far exceed the doses used in microdosing, seemingly resulting in several orders of magnitude more *activity* at the receptors. Additionally, in the cases of heart valve disease in Fen-Phen, all of the patients were symptomatic. Of the thousands of people who microdosed, no one has reported any heart valve trouble during their period of microdosing, and many people have been microdosing for over a year. All the people we have surveyed with heart problems had them before they started microdosing.

The problem, and it is a very real one, is that this article will be reviewed and popularized over the many different psychedelic and general media sites with varying degrees of accuracy. Since it is highly unlikely that large-scale long-term research necessary to investigate this possibility will ever be funded, the concern will never be validated or disproved. There were a number of frightening scenarios raised about psychedelics during the earlier research era, about LSD in particular, none of which were ultimately verified. However, their wide circulation led to considerable and unnecessary fears among millions of individuals using these substances. We need be careful not to create such fears before we have evidence. Given the serious and multiple warnings given out with most prescription medicine, that there might be unknown side effects to microdoses is to belabour the obvious.

We would look for an expansion of the receptor research (Question 7). It would be a great gift to all psychedelic research if studies could begin to go beyond measuring 5-HTP2A receptors and include, at least, the mTOR and TrkB signalling pathways as well (Ly et al., 2018).

A question to investigate is how the well-described accelerated neural plasticity of a number of psychedelics at high doses is diminished or intensified through periodic microdosing. Early speculation by Kornfeld (Kornfeld and Fadiman, 2013) has now been artfully demonstrated by the work of Ly's group (Ly, et al. 2018). This seems to be an especially fruitful area, given the growing body of research linking neural plasticity with both mental illness and recovery.

We are encouraged that in Question 8, the authors went beyond 5-HTP2A receptors and looked at peripheral tissues with doses well below behavioural thresholds as well. We hope the number and kinds of physical systems evaluated for effects continue to expand. For example, although it is now generally accepted that the number of neurons that exist outside of the brain exceeds the number within it, psychedelic researchers have not yet developed research methods to measure changes in gut neurons due to the effects of psychedelics or how those changes affect human biology and behaviour.

Finally, the issues of dose and schedule remain critical. While many pharmaceuticals have a given activity and that more or less of a dose leads to more or less of the same activity, this is not true for psychedelics at higher doses and far less so for microdoses. One size does not fit all, so that the identical dose, however calculated, will not yield the same results across individuals. This may be a hard problem, especially given the few research models popular in pharmacology in general. As for the effects of multiple doses over time, there has never been a suggested protocol that did not include days without dosing, in contrast to almost all psychiatric medications that warn of potential serious health issues if even a single dose is missed. For this and other reasons, psychedelics do not fit neatly into much of current psychopharmacology and thus need to be researched.

Our few concerns aside, these research proposals are a major step forward for psychedelics in general and microdoses in particular.

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Commentary

Torsten Passie

Psychedelics and creativity

I would recommend not mentioning just these very few anecdotal cases in respect to creativity and psychedelics. There are some good studies and reviews about the subject (Hartmann, 1969) on 40 prominent painters at the German Max Planck Institute of Psychiatry in Munich and the review on the subject by Krippner (1985).

When it comes to the very few studies looking for low doses of psychedelics and creativity (review in Passie, 2019), no study revealed any significant/relevant effects under controlled scientific conditions (e.g. McGlothlin et al., 1967). The study of Prochazkova et al. (2018) claimed (under weakly controlled conditions in respect to dosing and environment) increased lateral thinking, which has been discussed as a marker of creativity. This study employed doses of psilocybin that were above the perceptible level (4–8 mg p.o.). However, increased lateral thinking does not mean that the drugged subjects have shown increased creativity in a valid sense, e.g. creating more original painting.

Definitions: Microdosing and minidosing

I do not agree with the authors' narrow definition, since it does not reflect fully what is used in the literature and the appropriate Internet entries. It has been proposed that the term 'minidosing' could be used to separate the approach of taking small perceptible doses. It is also clear that many authors and Internet entries suggest the practice of just taking one dose at a time rather than a few ones consecutively as, for example, seen with the Fadiman scheme. This is also valid for taking a tenth or a twentieth of a usual dose. However, the issues related to definitions point towards the question/definition of what is considered a 'full dose'. In the case of LSD, some authors reasonably argue that 150 µg is a full dose (especially in females), whereas others consider 250 µg a full dose. This is a significant issue, because 15 µg is usually not perceptible by most subjects, but a dose of 25 µg is for most subjects (as shown in some scientific studies). Therefore, the definition has to be sharpened before scientific consensus can be reached and the evidence from so-called microdosers disseminated on the Internet as well as studies of anecdotal evidence (e.g. Johnson, 2018), which suffers from such inaccuracies, can be taken seriously.

Dosing of dried mushrooms

Plant/fungal material is generally quite unreliable for calculating a dose. I do not agree with the author's statement that 3.5 g *P. cubensis* is 'a usual recreational dose'. Most recreational users take 1 to 2.5 g as a recreational dose, which is also recommended in most books in the field. From my experience, and the research studies of Abramson and Rolo (1967), I would state that a dose of psilocybin below 3 mg is below the perceptible range. Usually, doses above this level can become apparent. For example, Prochazkova et al. (2018) used 4–8 mg psilocybin, i.e. more than a microdose, thus, more consistent with the definition of what might be considered a minidose.

The most used dosing regime and effects of micro- and minidosing

It can be easily seen in Internet entries that most subjects who take microdoses recreationally for 'bettering performance' take doses that give them some perceptible effects. Even a microdosing proponent like Paul Austin recommends doses where you can feel/perceive some alterations to some extent. How would you better your performance if nothing can be felt from a dose?

Following my comprehensive research into this topic (Passie, 2019), I have never come across anything about a 'workaholic approach' (dosing during weekdays, but not on weekends) as suggested by the authors. This also does not make much sense form a pharmacological point of view, because tolerance to LSD develops very quickly. Be reminded, that the US military has dosed soldiers with increasing daily doses to try to make them 'immune' to LSD's effects (Ketchum, 2006).

I think that a minidose (e.g. 20 to 50 µg LSD), in contrast to a microdose (which I define as something below 20 µg LSD, e.g. 5–15 µg), makes a significant difference in terms of recreational as well as scientific studies as it definitely alters psychological functioning and the cognitive system.

However, this alteration is not in any way equivalent to stimulants like Ritalin or amphetamine as is sometimes reported anecdotally. It is more a dissociation from the environment and the person itself. Cognitive abilities have been proven to be compromised in

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