RED LIGHT OREGON

Microdosing Safety And Recommended Usage Report For Measure 109

Introduction

We have conducted a literature review with the help of Dr. Rohit Singh, a Ph.D. Organic Chemist and a Research Assistant Professor in the Center for Drug Design in the University of Minnesota to assess the safety of long term activation of 5ht2b receptors by microdosing psilocybin as well as other potentially negative effects of microdosing

We have also looked into the recommended duration of a microdosing session and the duration of a microdosing protocol and who might benefit from microdosing.

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Microdosing Safety

5HT2B Long Term Activation

There have been concerns in the psychedelic community around the possibility of negative side effects of long-term microdosing Psilocybin due to activating the Serotonin 5ht2b receptor, which can cause health problems seen with people using the diet pill Fen-Phen. A literary review of academic research (a folder with all papers reviewed can be found here) uncovered that in order to get to a similar risk profile as Fen-Phen, which became significantly more dangerous at a daily dose of 60 mg one would need to consume at least 6 mg of Psilocybin on a daily basis. This dose is far beyond what is considered a microdosing dose which is 1-3 mg of Psilocybin. Currently, clinical trials are being done with a daily dose of 26 mg of fenfluramine, the substance in Fhen-Phen that was found to be dangerous at higher doses, which indicates FDA believes that a lower level of activation of 5ht2b receptor is safe. It is also common practice to not microdose every day but use different protocols like once every 2 days, or 4 days microdosing in a row and then a break for 3 days. Most microdosing experts also take a few weeks break from microdosing every few months to check in on themselves which increases the safety profile of microdosing psilocybin.

Dosages

	Drug	Typical Starting Dosage (Daily)	Max Recommended Dosage (Daily)
1	**Fenfluramine***	10 – 220 mg (Median = 60 mg)	60 mg (Less severe valvular heart disease)
2	**Phentermine**	15 – 60 mg (Median = 30 mg)	-
3	**Psilocin**	Microdosing 1-3 mg	-
4	**Psilocybin**	Microdosing 1-3 mg	-

Binding Affinity Values (Ki in nM)

For binding affinity, Ki values are presented in Table 2. All values are in nanomolar. For data points with multiple valuers available, Avg (n) represents an average of n Ki values.

Substance	5-HT2B
Fenfluramine	4,134.00
Nor-fenfluramine	Avg (2) 33.50
(+) Nor- fenfluramine	11.20
Phentermine	>10,000
Psilocin	4.60
Psilocybin	Avg(2) 349.35

Other negative side effects

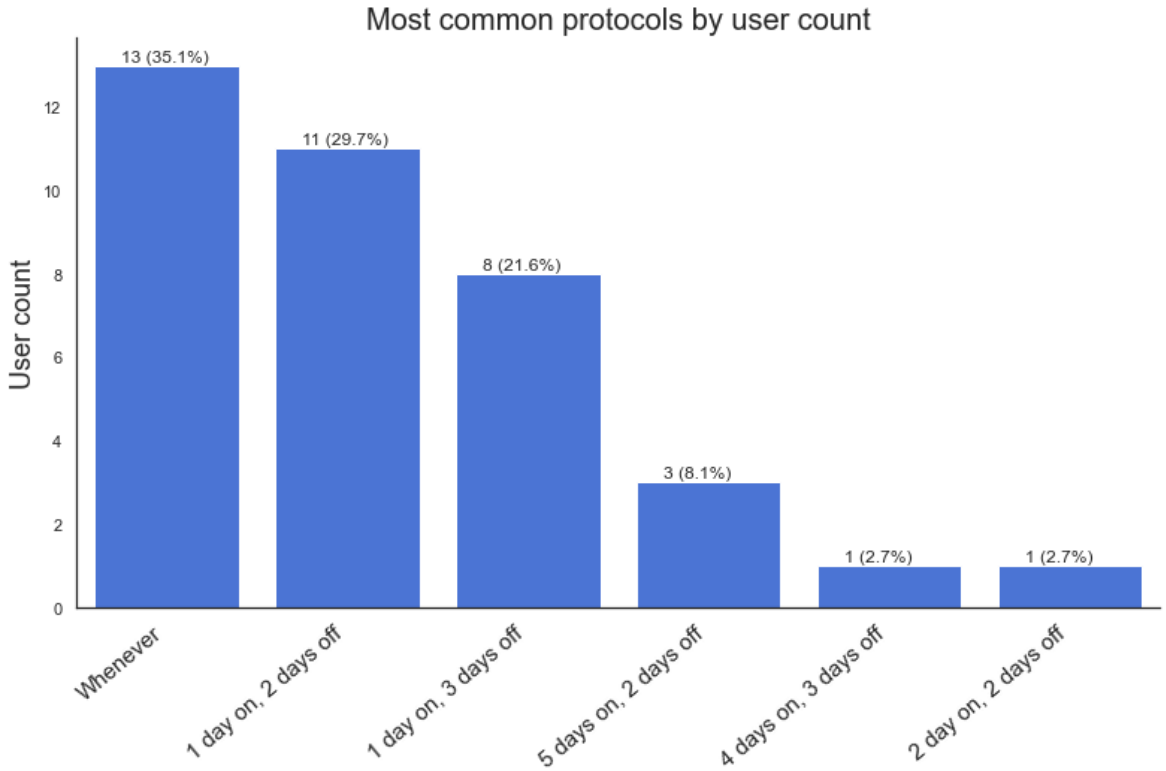
Negative side effects that occur with larger doses of psilocybin can also occur in smaller doses although to a lesser extent. These may include stomach discomfort, anxiety, impaired mood, and sleeplessness. These negative side effects are mostly acute and disappear after psilocybin has been metabolised. For many, these side effects can be addressed by decreasing the amount of Psilocybin or consuming the substance earlier in the day.

Duration of a Microdosing Session

A microdose of 3 mg of Psilocybin consumed orally has been shown to reach peak blood plasma concentration and peak intensity rating at 60 min. The intensity reported on 3 mg of psilocybin is quite low to begin with (4 out of 10) and goes down to near baseline by 2 hours (1 out of 10). Academic research conducted with microdosing conducted sessions of approximately 1.5 hours. It is important to note peak blood concentration may vary in the population and might change even depending on the amount of food consumed prior to consumption. Consuming psilocybin sublingual or using other novel mechanisms is likely to quicken the time to peak.

Duration & Frequency of a Microdosing Protocol

While some research has shown positive effects from the first dose, most research has focused on microdosing for a few weeks to a few months. Currently an 8 week long FDA clinical trial with psilocybin microdosing is being conducted. Generally, the frequency of microdosing is 2-4 times per week. Data from users on Red Light Holland iMicro app who consented to share their anonymized data revealed that most users prefer to microdose whenever they feel like it without a regular protocol(35.1%) followed by a 1 day on 2 day off protocol(29.7%), 1 day on 3 days off (21.6%) see graph for full data.



Resource Summary table

A folder with all papers reviewed can be found here.

	Source	Frequency/ Session length	Duration	Microdose Amount	Study Design
1	Kaertner, et. al. Nature Scientific Reports, 2021	Dosing with a psychedelic every third or fourth day (e.g., 2 times per week).	Over a period of 4, 5 or 6 weeks	0.1–0.5 g of dried psilocybin containing mushrooms	Online surveys and emails. The sample consisted of a cohort of volunteers planning to start microdosing in the near future.
2	Rootman, et. al. Nature Scientific Reports, 2021	1–4 times per week: 72.4% (n=2520) 5 or more times per week: 23.0% (n=800)	-	Dried mushrooms ≥ 0.3 g: 12.5% (n=435) 0.1–0.3 g: 71.6% (n=2497) ≤ 0.1 g: 15.9% (n=352)	A sample of self-selected microdosers (n = 4050) and non- microdosers (n = 4653) via a mobile application.
3	Kuypers, K. P. C. Ther Adv Psychopharmacol 2020	Frequency range between 2 and 4 times a week	For a few weeks, to months, or even years, although the latter is rare.	0.3–0.5 g of psilocybin containing mushrooms.	A review of 14 experimental studies from the literature.
4	Hutten, et. al. International Journal of Neuropsychopharmacology,	Frequency range between 2 and 4 times a week	-	0.5 g Psilocybin	Online survey. 1116 of the respondents were either currently microdosing (79.5%) or microdosed in the past (20.5%).

	2019				
5	Prochazkova, et al. Psychopharmacology, 2018	Approximately 1.5 hour long session	Single session	0.37 g of dried truffles	38 participants
6	Madsen, et. al., Neuropsychopharmacology, 2019	PET: 1 hr (43% 5-HT2AR Occupancy) Plasma psilocin concentration: 1 hr (maximum conc)	NA	3 mg Psilocin	1 participant
7	Moreno et al. 2006 Journal of clinical psychiatry	8 hours for testing	4 single doses with different dose 1 a week	Microdose 1.7 mg per 70kg	7 participants

Who Could Benefit From Microdosing?

While there have been only a few placebo-controlled microdosing studies most of which conducted with a non-clinical population it is worth noting a double-blind placebo-controlled study with 7 subjects with DSM-IV-defined OCD found a reduction in OCD symptoms after microdosing as little as 1.7 mg per 70 kg (Moreno et al., 2006). Furthermore, at quasi-experiment in a retreat setting assessed the acute (90min) effects of a single microdose found both convergent (which requires identification of a single solution to a well-defined problem), and divergent (which requires the collection of many possible solutions to a loosely defined problem) thinking improved, (Prochazkova et al., 2018).

Numerous self-reporting studies have found improved mood, cognition, and creativity, which often served to counteract symptoms especially from conditions of anxiety and depression. For a comprehensive list of such studies, we recommend Vince Polito's preprint, The emerging science of microdosing: A systematic review of research on low dose psychedelics (1955 – 2021) and recommendations for the field which further summarised 44 microdosing research papers. The authors recommend that given that one of the most consistent findings amongst the papers is that microdosing is associated with identifiable subjective drug effects, researchers should avoid describing microdosing as sub-perceptual. Instead, they suggest that acute subjective effects should always be measured and microdosing could be defined as sub-hallucinogenic with no loss of functionality.

Data from 115 users on Red Light Holland iMicro app who consented to share their anonymized data revealed that for every 5 year age decrease (or decrease in age group), people are 11% more likely to want to microdose to increase focus. This fits the global trend of younger people struggling with focusing their attention and presents the possibility that microdosing might help prevent some of the abuse of stimulants in our society.

Market research we have conducted in Oregon based on Oregon demographic shows that 16% of adults in Oregon would like to receive microdosing services on at least a weekly basis. The full report can be found here.

It is further worth noting a few more microdosing LSD placebo-controlled experiments. Due to the similarity of neural action between Psilocybin and LSD, both activating the 5ht2a receptor, these experiments might shed light on the benefits of Psilocybin as well. One such paper found statistically significant stimulant effects and trends for energy and intellectual efciency (Murray at el., 2019). The same paper found a reduction of oscillatory power across frequency bands indicative of broadband cortical desynchronization. This Desynchronization effect is similar to the desynchronization seen in higher doses of 5ht2a agonist and is indicative of the brain diffusing its prediction mechanism and entering into an extra plastic state.

Another paper found increased pain tolerance while microdosing (Ramaekers et al., 2021) indicating that microdosing might be helpful in solving the opioid epidemic.

Holze (2021) found subjective reports of "good drug effect" with doses as little as 1/10 th of a recreational dose and Hutten (2020) found doses as low as 1/20 of a recreational dose enhances sustained attention and affects mood states in positive directions. This shows Microdosing might help people with ADHD and Depression.

Conclusions and Recommendations

- Based on relevant placebo controlled research people suffering from OCD, depression, attention problems and pain might benefit from Microdosing and based on market research 16% of Oregon's adult population is interested in Microdosing services on at least a weekly basis.
- Microdoses should be clarified in regulation to be no more than 3 mg of Psilocin or the equivalent psychoactive material that breaks down into 3 mg of Psilocin.
- Microdosing facilitator supervised session time should be approximately 1.5 hours but facilities should allow clients to stay for longer if they so wish.
- Due to the low intensity of microdosing and in order to accommodate facilitators wanting to provide educational support services such as mindfulness, meditation and somatics at a price point that is equitable, a maximum ratio of 16 clients to 1 facilitator is recommended. This is the ratio recommended by the National Center for Educational Statistics in the United States between college students and teachers.
- One intake session should be clarified to be enough for 6 months of microdosing service received up to 5 times a week. After which a client should be encouraged to take a few weeks break from microdosing and go through a new preparation session to check if they should continue to microdose.