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The Synthetic Toad – How to investigate 5-Meo-DMT in the lab

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Introduction: The venom of Bufo alvarius, the Colorado River toad, known as 5-MeO-DMT, is used across the globe to elicit strong psychedelic experiences. While many who consume the substance collect it from live toads, there has been a recent shift towards using synthetic formulations of 5-MeO-DMT.
I spoke to Johannes Reckweg, who conducted one of the first laboratory studies administering a synthetic 5-MeO-DMT formulation to human participants:
Reckweg J, Mason NL, van Leeuwen C, Toennes SW, Terwey TH, Ramaekers JG. (2021) A Phase 1, Dose-Ranging Study to Assess Safety and Psychoactive Effects of a Vaporized 5-Methoxy-N, N-Dimethyl-tryptamine Formulation (GH001) in Healthy Volunteers. Front Pharmacol. 2021 Nov 25;12:760671. doi: 10.3389/fphar.2021.760671.

Lukas Basedow, M.Sc.: What did you want to find out with this particular study?

Johannes Reckweg, M.Sc.: Our primary aim was to look at the safety and tolerability of different doses of 5-Meo-DMT as well as its different psychoactive and cognitive effects in a controlled setting. I do want to mention that we used a 5-MeO-DMT formulation called GH001 as this was a commercially funded study, but going forward, I will just say 5-MeO-DMT or 5-MeO. We wanted to look at this because most previous data come from observational studies or reports from the internet, so they are not from controlled environments or involve unknown doses. That was the main goal — to investigate the effects in a controlled setting. Secondly, we wanted to look at which doses elicit a peak experience. These experiences are commonly defined by an intense state of ego dissolution, and 5-MeO seems to reliably elicit these effects. These peak experiences seem to predict therapeutic effects, so we wanted to explore which dose or setup would provide the best method for achieving such an experience.

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LB: Why are you specifically investigating 5-MeO DMT? What is unique or exciting about this substance?

JR: It has a few interesting properties. Mainly, it has an immensely fast onset. Usually, it is smoked or vaporized, then inhaled and works immediately within a few seconds. It is also very short acting compared to other psychedelics like psilocybin or LSD, which last several hours. In comparison, 5-MeO-DMT only lasts for about 15 minutes and after 30 minutes participants usually feel quite sober again. However, the effects during that short timeframe are often very, very intense. Another aspect is that it seems to have functional dominance for the 5-HT1a receptor, while other psychedelics are less selective or rather exert their effects through the 5-HT2a receptor, which could provide interesting avenues for further research.

LB: Could you give us some detail regarding the experimental setup? For example, the dosages involved etc.

JR: We first had a medical and psychological screening procedure to ensure that participants were in the right mindset. If enrolled, participants were invited for a test day on which the substance was administered, a one-day follow-up via telephone, and finally, a seven-day follow-up. In the first part of the study, we used four individual doses of 2mg, 6mg, 12mg, and 18mg and had four participants assigned to each dose. After each dosing group, we had a meeting with a safety group to determine if it would be safe to go on with the next dose. We also had the potential for intermediate steps. So, while the main doses were 2, 6, 12, and 18mg, we also had the possibility to include 4, 9, and 15mg. Just to make sure that if we needed smaller steps, they would be in place. We did not need this in the end since all dosing steps were considered safe. In the second part of this study, we applied an individualized dose regimen, which means that we had an up-titration of doses. While in the previous part, participants received one of four doses on their test days, in the second part, each participant received first 6mg, then 12, and then 18, interspaced at 3 hours on the same day. After each dose, we evaluated whether the participant had reached a peak experience or not, based on a questionnaire and evaluations of the team and the present medical expert. If the participant did not achieve the peak experience, we moved on to the next dose.

LB: Can you give some more detail on the experimental setup in terms of the room, decorations, smoking equipment, etc.?

JR: The sessions took place in a large, fairly empty room. There were some tapestries on the walls to make it feel a bit cozier. The room was equipped with foam mattresses on the floor and a regular mattress on top, as well as blankets and pillows, to make it comfortable. There were also chairs on the side for the medical doctor and the team to sit on. The drug was vaporized into a balloon from which the participant inhaled. We practiced this inhalation with the participant before the actual session, so that they could get a feeling for it. After inhaling from the balloon, participants held their breath for 10 seconds while I counted down, after which we asked them to lie back, for safety reasons. As I mentioned before, this substance works basically immediately, and we wanted to minimize any risks for the participants. In total, we spent about an hour in that room, just so that we could make sure that all the effects had completely passed. I would say that participants were typically in an altered state for about 15 to 20 minutes.

LB: You already mentioned that you used different dosages in this study. Could you comment on the size of these dosages? Are there comparable dosages for other psychedelics?

JR: This is actually difficult to assess compared to other substances. We based the dosages on experience reports from the internet. We looked through many of these online reports, and we have done naturalistic studies where we tried to record the dose if it was known.1 Unfortunately, these naturalistic reports are not that useful since people mostly consume the toad secretion instead of the synthetic formulation we used in our study. Therefore, we decided to increase our dosages only in small steps and used 2 mg as a first, very small starting point. With 6 mg, participants definitely noticed stronger effects, usually nausea or feeling a bit dizzy, but also some slight psychedelic effects, which indicates a small to moderate dose. 12 mg can be considered a moderate dose. While we did see some peak experiences here, other participants only had a rather mild experience. Based on our participant reports, the last stage of 18 mg can be considered a large dose. But we saw large interpersonal differences at each dose from 6 mg upwards, making comparisons to other psychedelics difficult.

LB: You already mentioned some of your results, but could you summarize the key findings again?

JR: The most important point here is really that all conditions and dosing levels were deemed safe and tolerable by the attending group of experts and medical doctors. We did not see any changes in cognitive domains or well-being from baseline compared to the end of the study. Regarding the elicitation of a peak experience, the individualized dosing seems to be the most reliable, as we achieved a peak experience in each of the four participants in this condition. We think this might be the way to go with this substance in the future: Slowly increasing the dosage to find the one that is sufficient for each individual.

LB: Why do you think there is such a large individual difference in the dose needed to achieve a peak experience?

JR: That is a very good question, and I can just speculate here because there is a plethora of possible reasons. One factor could be previous experience with psychedelics, especially if the participant has had a previous peak experience. This could potentially pave the way to get back into the same mental state.

LB: Did your participants have previous experience with psychedelics?

JR: Yes. We did this study in healthy volunteers who needed to have at least two prior experiences with psychedelics. Another reason could be personality factors like openness or a low level of neuroticism. Because of the fast and intense action of 5-MeO-DMT, it involves a strong component of relinquishing control. There is no increase working towards a peak, it literally starts at the peak, which can be quite a shock to participants. If they are not used to that, they might try to stay in control, which could make it more difficult to achieve this peak. Another factor that might influence the ability to achieve this peak is previous meditation training, but again, that is just speculation.

LB: Those are some interesting ideas! In a previous interview, I talked to Dr. Dea Stenbaek, who discussed her research showing that the level of 5-HT2a receptor binding can predict the subjective mystical effects of psilocybin. Do you think something similar could play a role here?

JR: Interesting question, but I am unaware of any data on this with 5-MeO-DMT in humans. One complication is that most neuroscientific psychedelic research focuses on the 5-HT2a receptor, while 5-MeO-DMT has a strong affinity for the 5-HT1a receptor.

LB: You mentioned that you used synthetic 5-MeO DMT in your study and that there is a natural source as well. Could you comment on the advantages or disadvantages of using either the synthetic or the natural version?

JR: Natural 5-MeO-DMT is usually harvested through milking the *Bufo alvarius* toad [also known as Colorado River or Sonoran Desert toad]. Milking a toad can put them under a lot of stress because the secretion is a defense mechanism. The venom is collected, dried, and then smoked. Of course, this venom contains not only 5-MeO-DMT but also other potentially psychoactive substances, which might interact in their effects. This is called the entourage effect. Proponents of using the toad secretion say that you need all the components in the venom to achieve the proper effects. However, so far, it is unclear if this entourage effect really exists here and, if so, how much of a role it actually plays. You also have to take into account the environmental impact of putting these toads under so much stress, especially with psychedelics getting into the forefront of mainstream media. My colleague Malin Uthaug actually started an initiative called "Save a toad, Exploit a chemist," which advocates for using synthetic 5-Meo-DMT instead of the toad venom. Finally, from a scientific standpoint, you have more control over the purity and quality of the substance if you use synthetic 5-MeO-DMT. You know exactly where it comes from, you know the dose, and the situation becomes much more controlled compared to using the toad venom.

LB: You said that this study was mainly done to assess safety and tolerability in healthy participants. How do you evaluate the potential of using 5-MeO DMT in therapeutic settings and given the unique characteristics of this substance, how would this therapy look like?

JR: We have actually completed a study in patients with treatment-resistant depression recently, and a first look indicates that this substance has therapeutic potential. However, the question of an appropriate treatment regimen still needs to be explored. In contrast to psilocybin-assisted therapy, there was no concurrent therapy in our study. Because of the unique effects of 5-MeO-DMT, it would be very difficult to conduct therapy while patients are under the influence since most of them would be non-responsive. Nonetheless, we did see a strong and pronounced therapeutic effect in this clinical study.2

LB: One final question: The study we are discussing was funded by a company instead of a university or funding agency. What role do you see for pharmaceutical companies in the future of psychedelic research and therapy?

JR: Research and therapy might be possible without pharmaceutical companies, but it would take a lot more time and effort. The work that non-profits like MAPS or MIND are doing and have done, really laid the groundwork, and we need to build on that and explore all possible options. This field has been stigmatized for a long time, after research in the 70s and 80s came to such an abrupt stop. It is good to see that there is renewed interest now. However, money is needed to drive research forward in any field, as you could see with MAPS and how long it took them to get their studies approved. With psychedelics being at the forefront, it is now easier to get funding to do this research, but mainly to investigate the therapeutic application of the major substances, like psilocybin or MDMA. If you want to look at other, less popular substances, like 5-MeO-DMT, this commercial funding is necessary to kick-start the research landscape. Of course, we hope that the industry will not exploit this and that psychedelics will be accessible if they become approved, regulated drugs. Many psychedelics are naturally available from plants and animals — the clinical, synthetic versions of these substances should also be available to the people that may benefit from them.

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