# Preclinical Studies on the Anti-Obsessional Properties of Psilocybin

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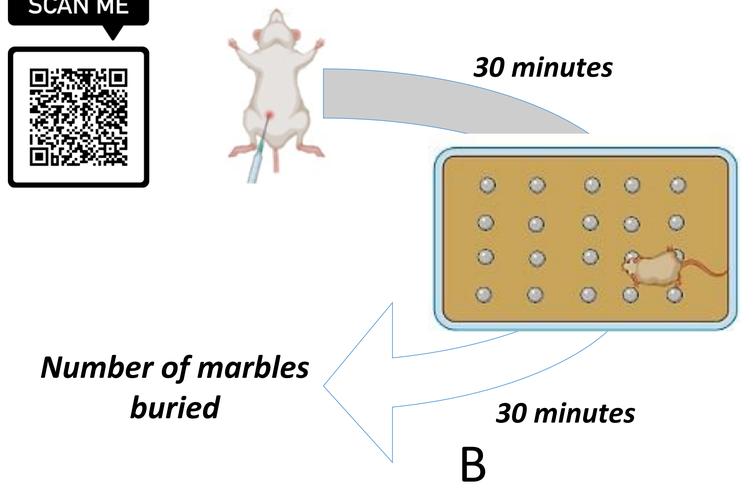
## BACKGROUND

- There is increasing interest in the potential role of psychedelic compounds in the treatment of psychiatric disorders.
- Obsessive compulsive disorder (OCD) is characterized by obsessional thoughts and compulsive behaviors.
- Notwithstanding the relative efficacy of serotonin uptake blockers and cognitive-behavioral therapy (CBT), a third or more patients with OCD do not respond to standard treatments.
- Reports from one clinical trial and several preclinical studies suggest that 5-HT2A receptor agonists with psychedelic properties may have unique efficacy in the treatment of OCD.
- We are examining the effect the psychedelic agent, psilocybin (PSIL), on marble burying (MB), a rodent proxy of obsessional behavior, using psychedelic and sub-psychedelic doses as determined by the head twitch response in mice.
- In addition, we are conducting a series of experiments to determine the role of 5-HT2A, 5-HT2C and 5-HT1A receptors in the anti-obsessional effect of PSIL.

## METHODS

- Male ICR mice (30±2 gm) were group housed under a regular 12 hr. light dark cycle. Drugs were administered by intraperitoneal (i.p.) injection 30 minutes before assessment of MB.
- Psilocybin (PSIL) was administered at a dose of 4.4 mg/kg i.p. alone, or preceded by the 5-HT2A receptor antagonist, M107900 (2 mg/kg i.p.), the 5-HT2C receptor antagonist and the 5-HT1A receptor agonist, 8OH-DPAT (2 mg/kg i.p.).
- Escitalopram (ESC, 5mg/kg i.p.) was administered as a positive control. Marble burying was measured 30 min. later.
- In this test each animal is introduced into a cage in which 20 marbles are situated on top of the sawdust. Over30 minutes, the number of marbles buried by the animal is counted.
- Statistical analysis compared cumulative MB over a 30-minute period among the different treatment groups by ANOVA and post-hoc tests.

SCAN ME

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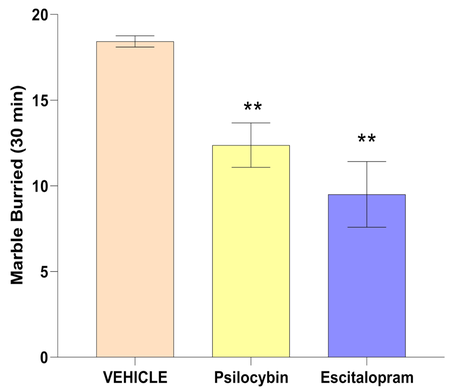


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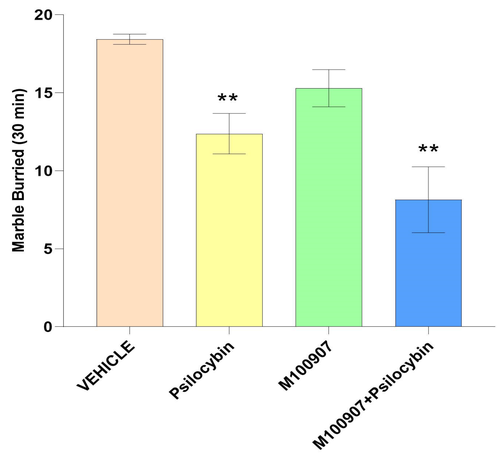


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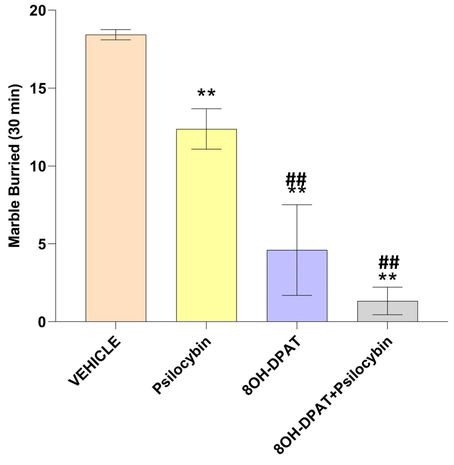


**Figure**: Effects of psilocybin on marbles buried during the total duration of the MB test

(A) Psilocybin (*4.4 mg/kg*) significantly decreased total number MB as did escitalopram.

(B) The 5-HT2A antagonist, M100907, did not significantly alter the effect of psilocybin MB.

(C) The 5-HT1A agonist**,** 8-OH-DPAT significantly decreased total number MB and may be additive to the effect of psilocybin

** $p < 0.01$, significantly different from the vehicle (VEH) control. Number of mice in treatment groups 5-16.

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## RESULTS & DISCUSSION

- Both ESC 5mg/kg and PSIL 4.4 mg/kg induced a significant reduction in cumulative number of marbles buried over a 30-minute period as compared to vehicle (VEH) ($F=6.4$, df 2, 30, $p=0.004$; ESC vs VEH $p=0.01$; PSIL vs. VEH $p=0.009$). Lower doses of ESC and PSIL were not effective.
- Our results suggest that the 5-HT1A receptor agonist, 8OH-DPAT, reduces MB and that this effect may be additive to PSIL.
- There was no significant effect of the 5-HT2A receptor antagonist, M107900 on the PSIL-induced reduction in MB.
- Our finding is in accordance with prior reports that PSIL induces a significant reduction in MB in mice over a 30-minute period and that this effect may not be mediated via the 5-HT2A receptor .
- It is noteworthy that our finding was observed at a higher dose of PSIL than previously reported by Odland et al (2021) (4.4 mg/kg in our study in male ICR mice vs. 1.0-2.0 mg/kg by Odland et al in female NMRI mice).
- However, Matsushima et al (2009) observed a significant effect on MB with 1.5 mg/kg PSIL in male ICR mice. Thus, the role of gender and strain effects on the anti-MB effect of PSIL in mice remains to be further evaluated.
- Overall, our findings support a key role for the MB test in screening psychedelic compounds for a potential role in the treatment of OCD.

## REFERENCES

**[1]** Odland AU, Kristensen JL, Andreasen JT. Behav Brain Res. 2021 Mar 5;401:113093.

**[2]** Matsushima Y, Shirota O, Kikura-Hanajiri R, Goda Y, Eguchi F. Biosci Biotechnol Biochem. 2009 Aug;73(8):1866-8..

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