

## 1. Title

**Psilocybin reduces alcohol intake in females independently of the estrous cycle and is potentiated by RS-baclofen**

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## 4. Precise description of objectives

Psilocybin is emerging as promising treatment for Alcohol Use Disorder (AUD). However, the influence of the estrous cycle on its efficacy has not been investigated, despite known fluctuation in the expression of 5-HT<sub>2A</sub> receptors, its primary pharmacological targets, across the cycle.

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The present study aimed to determine whether psilocybin reduces alcohol consumption independently of the estrous cycle stage in a female preclinical model of AUD, and to evaluate its therapeutic potential in combination with RS-baclofen. No previous study has assessed the efficacy of a psilocybin/RS-baclofen combination in AUD.

## 5. Material and methods

Adult female Long-Evans rats (n = 17) were exposed to intermittent access to 20% ethanol for 1 month, followed by chronic operant self-administration for 5 months (15 min sessions, 5 days/week).

Psilocybin (5 mg/kg, i.p.) or saline were administered 4 hours prior to self-administration sessions. The estrous cycle stage was determined using vaginal smears collected at fixed time points before, during, and after testing.

In the combination study, psilocybin (5 mg/kg, i.p.) was administered first, followed 3.5 hours later by RS-baclofen (1.5 mg/kg, i.p.) given 30 minutes prior the session.

## 6. Results and conclusion

Psilocybin significantly reduced alcohol consumption in females (-47.6%).

This effect was observed across all phases of the estrous cycle, indicating that psilocybin reduces alcohol consumption regardless of cycle stage, although the magnitude of the effect was greater

in proestrus (-69%, d = 3.03) than in estrus (-47.8%, d = 2.69) or diestrus (-62.2%, d= 2.02). Data for metestrus were less conclusive because this phase is brief resulting in fewer observations.

The psilocybin/RS-baclofen combination enhanced the reduction in alcohol intake (-69.9% vs -50.9%), although this difference did not reach statistical significance (p=0.063).

These findings support psilocybin as a promising therapeutic strategy for AUD in females, with robust efficacy independent of the estrous cycle and additional potential when combined with other pharmacological approaches.

#### **7. Declaration of interest and funding**

The authors declare no conflicts of interest.

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