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NIH Heterogeneous Stock rats trained to heroin self-administration show heterogeneous response to the anti-addictive effects of the MOP/NOP agonist Cebranopadol

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Background/rationale: Cebranopadol is a novel MOP/NOP agonist with low abuse liability, making it a potential candidate as pharmacological therapy for opioid use disorder (OUD). In light of the heterogeneous treatment response shown by OUD patients, we tested the effect of Cebranopadol on heroin self-administration (HSA) and cued relapse (CR) in NIH heterogeneous stock (HS) rats subjected to a multisymptomatic model of OUD.

Hypothesis: HS rats would show heterogeneous response to the effects of cebranopadol.

Results: 795 (389 female) HS rats were screened and allocated into OUD-vulnerable, -resilient, and -intermediate clusters as we previously described (PMID:34975564). The effect of cebranopadol (0, 12.5, 25, 50 µg/kg) on HSA and CR was tested on 42 males (18 resilient, 17 intermediate, 7 vulnerable) and 38 females (5 resilient, 14 intermediate, 19 vulnerable).
Cebranopadol significantly ($p<0.0001$) reduced HSA in all three female clusters. In males, Cebranopadol reduced HSA in the resilient ($p<0.001$) and intermediate ($p<0.001$), but not in the vulnerable cluster due to two rats out of 7 that did not respond.

Cebranopadol decreased CR in all three clusters of both male and female rats. Also in this case we found 6 males and 6 females (heterogeneously distributed among clusters) that did not respond to cebranopadol.

Discussion: Globally, cebranopadol showed marked efficacy on HSA and CR in HS rats. Few rats, independently from the belonging cluster did not respond to the drug. Sub-clustering and genetic analysis are underway to further evaluate if there are behavioral and/or genetic traits predictive of lack of sensitivity to cebranopadol.