REL-1017 (esmethadone) Showed No Reinforcing Properties Compared to Oxycodone in Rat Self-Administration Study

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BACKGROUND AND AIM

REL-1017 (esmethadone; dextromethadone) is a safe and well tolerated[1] novel uncompetitive NMDAR channel blocker with a preference for pathologically hyperactive GluN1-GluN2D NMDAR channels[2]. REL-1017 has twenty-fold lower affinity at the mu-opioid receptor than levo-methadone[3] and lacks clinically meaningful opioid agonist actions[4-6]. REL-1017 is currently in Phase 3 trials for the treatment of Major Depressive Disorder[7].

Oxycodone is a mu opioid agonist drug and a Schedule II controlled narcotic with known abuse potential.

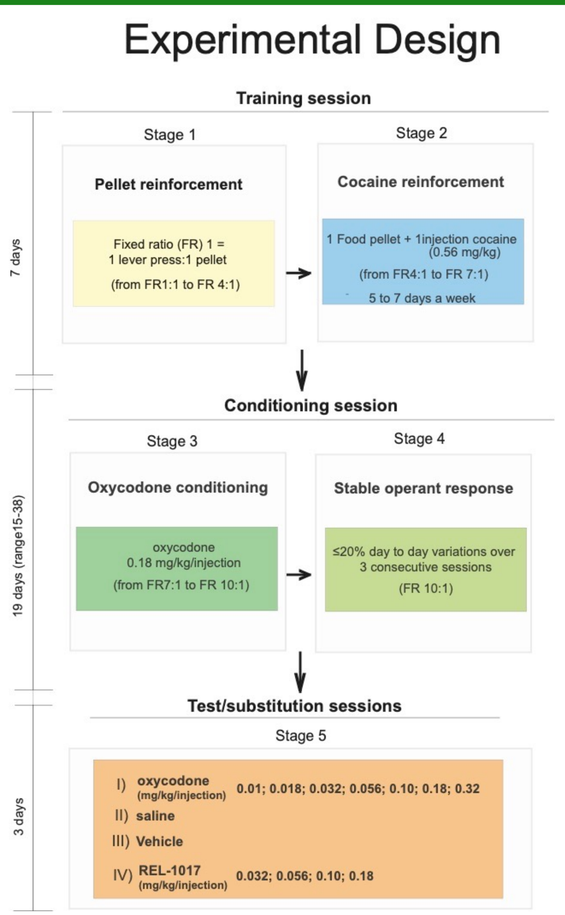
The objective of this study was to assess the relative reinforcing efficacy of REL-1017 in Sprague-Dawley rats conditioned to self-administer oxycodone during daily access periods.

Three-day substitution test sessions were instituted in rats trained to self-administer oxycodone intravenously. Complete substitution was defined as drug-maintained lever-press responding for three consecutive days at levels similar to those maintained by oxycodone.

*Criteria for Establishment of the Test Item being Ineffective as a Reinforcer**
"If responding, as measured by the total number of injections, declines over the course of the three-day substitution period or there are "vehicle-like" or "saline-like" response topographies during the course of testing (e.g. a downward staircase pattern), then the test article will be considered lacking reinforcement properties."

*study protocol

STUDY DESIGN



RESULTS

Figure 1

In animals with stable self-administration of oxycodone for the previous 3 days, test sessions were instituted where oxycodone was substituted with: saline; oxycodone (0.01; 0.018; 0.032; 0.056; 0.1; 0.18; 0.32 mg/kg/injection); vehicle; or REL-1017 (0.032; 0.056; 0.1 and 0.18 mg/kg/injection). All of the positive control groups exposed to any oxycodone dose maintained a stable number of infusions over 3 days (p=ns between injections at day 1 and 3 for all dosing groups). As expected for non-reinforcing stimuli in this assay, saline, vehicle and all REL-1017 doses showed a typical "extinction burst" pattern of responding, characterized by an initial rapid increase of lever-pressing on the first day followed by a downward staircase pattern of responses on the second and third day (*=p<0.05, **=p<0.01 between injections at day 1 and 3 for all dosing groups, including the vehicle group; n=6 for each group). REL-1017 at all tested doses showed a pattern comparable to vehicle.

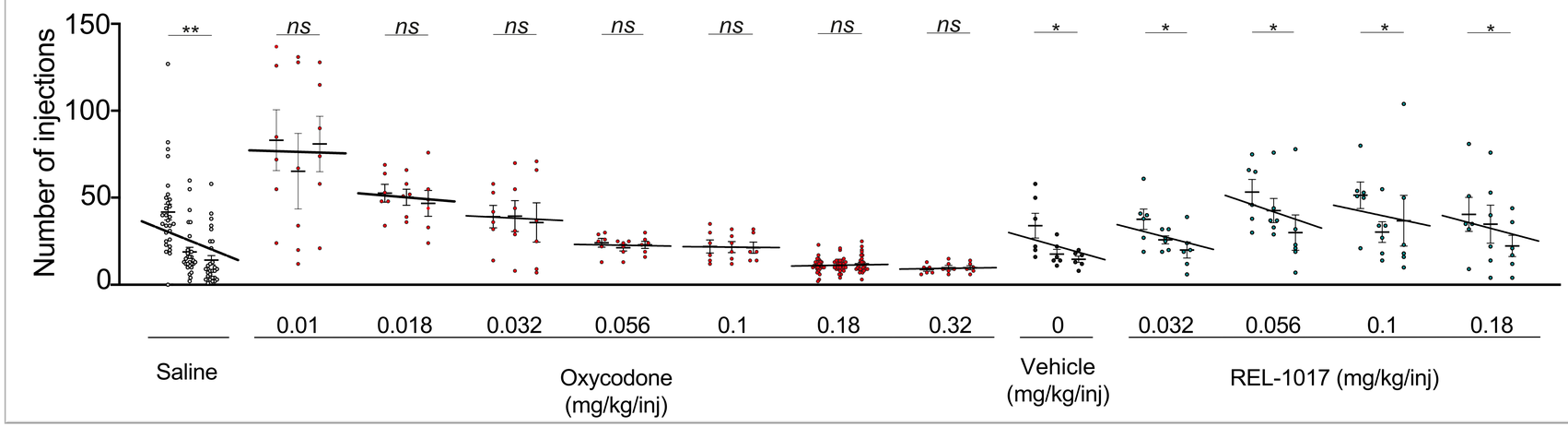
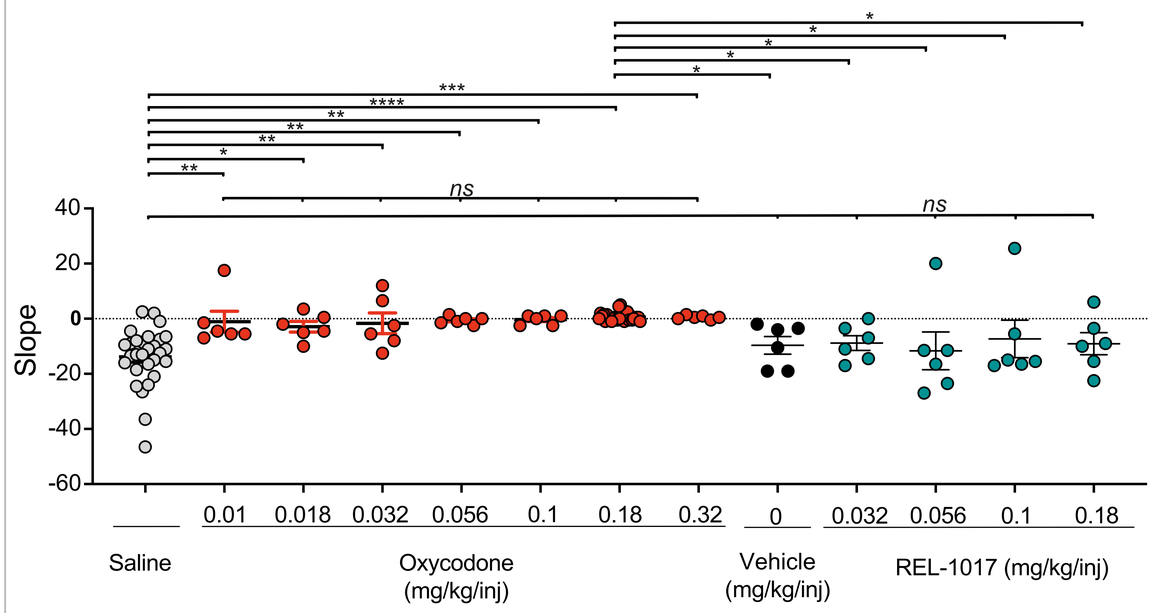


Figure 2

The graph shows the differences in the day-to-day pattern of injection during the test session and the linear regression functions (slopes) fitted to the total number of injections during each three-day interval calculated for each study item. The calculated slopes for saline, vehicle and REL-1017 at all doses were not statistically different between each other. The calculated slopes for saline, vehicle and REL-1017 at all doses were all statistically significantly different when compared to oxycodone (*=p<0.05; **=p<0.01; ***=p<0.001;****=p<0.0001). For all 4 doses of REL-1017 tested in this study the day-to-day intakes demonstrated a downward staircase pattern of intakes resulting in negative sloped linear functions (saline= -13.83; vehicle= -9.667; RE-1017 0.032 mg/kg/injection = -8.833; REL-1017 0.056 mg/kg/injection= -11.67; REL-1017 0.1 mg/kg/injection= -7.333; REL-1017 0.18 mg/kg/injection= -9.083). For the seven tested doses of oxycodone, the day-to-day intakes demonstrated a stable pattern of intakes resulting in neutral sloped functions (oxycodone 0.01 mg/kg/injection= -1.083; oxycodone 0.018 mg/kg/injection= -2.917; oxycodone 0.032 mg/kg/injection= -1.667; oxycodone 0.056 mg/kg/injection= -0.5833; oxycodone 0.1 mg/kg/injection= -0.3333; oxycodone 0.18 mg/kg/injection= 0.569; oxycodone 0.32 mg/kg/injection= 0.5).



CONCLUSION

Self-administration of REL-1017 in all dosing groups declined over the course of the three-day substitution period. The "vehicle-like" and "saline-like" downward staircase pattern over three days indicates that REL-1017 lacks reinforcing properties in this experimental setting, in contrast with the positive control oxycodone.

These data in rats are compatible with prior research indicating the lack of abuse potential of REL-1017[4,5] as recently affirmed by the DEA: *The d-isomer lacks significant respiratory depressant action and addiction liability*[6].

REFERENCES

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DISCLOSURES

This research was performed at Charles River Laboratories and was sponsored by Relmada Therapeutics. Dr Gauvin is an employee at Charles River Laboratories. Drs. Manfredi, Pappagallo, Caron, Folli, Henningfield, Ashworth, Lanier are paid consultants of Relmada Therapeutics. Dr. Manfredi is an inventor on esmethadone patents and other patents and patent applications. We are grateful for the contributions of *Dr. Reginald ("Reggie") V. Fant in our efforts to study and understand the potential of REL-1017 for abuse. We were deeply saddened by his unexpected death in September 2020.

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