Evaluation of the abuse liability of oxycodone in male and female rats using two approaches: intravenous self-administration and conditioned place preference

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Background

In collaboration with the NIH HEAL Initiative Preclinical Screening Platform for Pain (PSPP), we evaluated the abuse liability of oxycodone in the intravenous self-administration and conditioned place preference tests in male and female Sprague Dawley rats.

Methods

Study 1: Intravenous self-administration:

In the self-administration study, an independent group design (N=11-13 in each group) was used for both genders. Drug self-administration took place in sound attenuated operant chambers (Med Associates, VT) where rats (275-299 grams for male and 175-199 grams for female at arrival) pressed an active lever that delivered the test compound intravenously through a jugular vein catheter. Rats were allowed to self-administer saline (negative control), morphine (0.6 mg/kg/infusion) or oxycodone (0.01, 0.03, 0.06 and 0.1 mg/kg) by pressing the active lever on a fixed ratio 3 (FR3) schedule for 1 hour/day. Acquisition training lasted 20 days.

Progressive ratio (PR) schedule is a paradigm in which animals face progressively lower chance to get reward. The 1-hour PR test was performed the next day after the final day of acquisition training.

Study 2: Conditioned place preference (CPP):

In the CPP study, an independent group design (N=16) was used for both male and female rats with five treatment groups (saline, cocaine 15 mg/kg, and oxycodone 1, 3 and 5 mg/kg were injected intraperitoneally). Perceptive cues were applied to create a distinctive texture and visual features for the two compartments.

A 10-day protocol was used in this study. Day 1 was baseline day in which the door between the two compartments was open and the rats were allowed to explore for 20 minutes. Days 2-9 were conditioning days in which rats were treated with saline on days 2, 4, 6 and 8, and with either cocaine or oxycodone on days 3, 5, 7, 9. Animals were confined in the "drug compartment" or "saline compartment" immediately after drug administration for 20 minutes. On Day 10, all rats were allowed to explore the testing arena freely for 20 min, with door open. There was no drug administration on Day 10. Rats were video-taped at Day 1 and Day 10, and their time in each compartment was measured by experienced researchers who were blind to treatments.

PSPP is currently accepting assets for evaluation
For eligibility and participation inquiries, contact:

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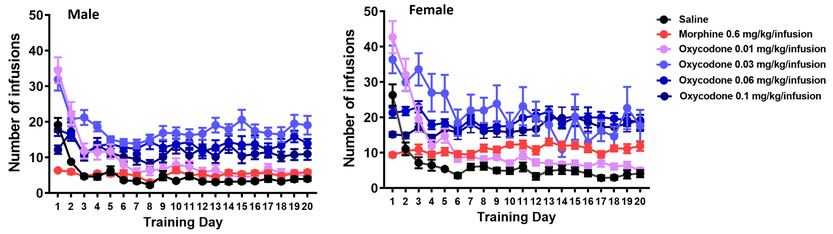
For more information about PSPP, visit (or scan the QR)
https://pspp.ninds.nih.gov/

National Institute of Neurological Disorders and Stroke

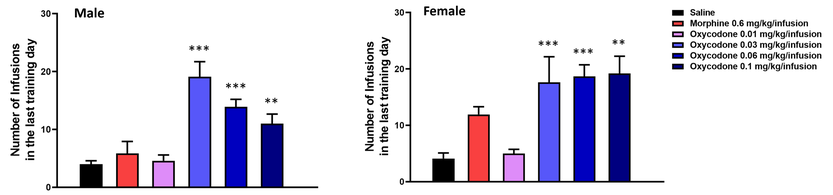
NIH - Helping to End Addiction Long-term
https://heal.nih.gov

Study 1: Intravenous Self-Administration

Number of infusion with FR3:

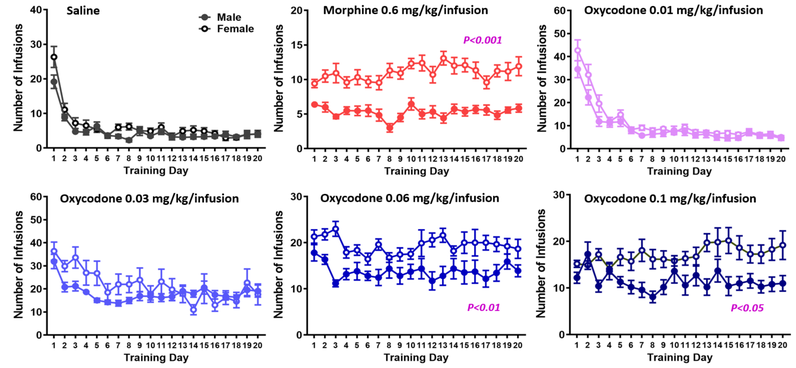


The compound infusions in different treatments / doses in male and female rats across 20-day acquisition training session.



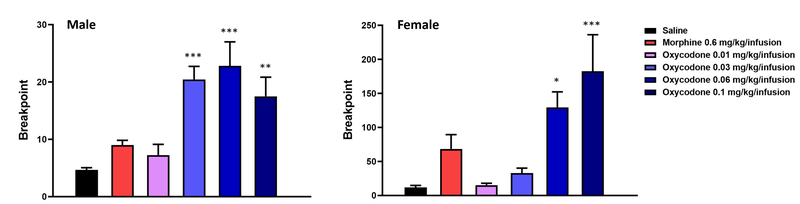
*Number of infusions in the last session (day-20) of acquisition training. One-way ANOVA with Dunnett's post-hoc test. **: p<0.01 and ***: p<0.001 vs saline group. Data are presented as mean ± sem.*

Male vs. female rats on number of infusion:

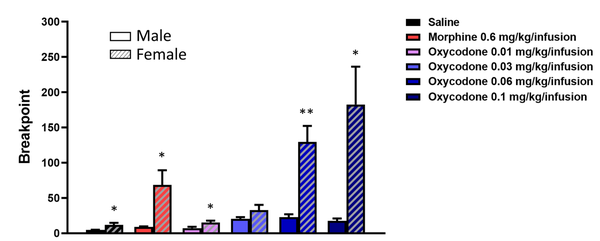


The data suggested that female rats had tolerance to higher dose of abused compounds (cocaine and oxycodone here). Data are presented as mean ± SEM.

Breakpoint with progressive ratio (PR) schedule:



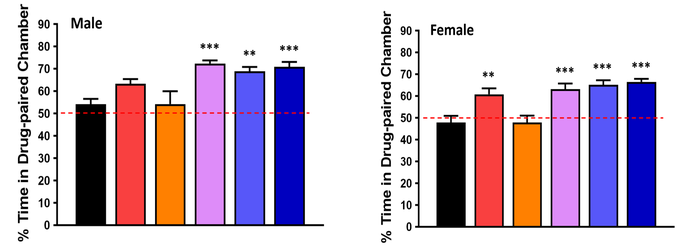
Breakpoints is defined as the finial progression ratio that causes drug infusion in a PR session (:p<0.05; **: p<0.01; ***: p<0.001 vs saline group. Data are presented as mean ± SEM.).*



A comparison between male and female rats' breakpoints in PR schedule. Student's t-test was used. (: p<0.05; **: p<0.01. Data are presented as mean ± SEM.)*

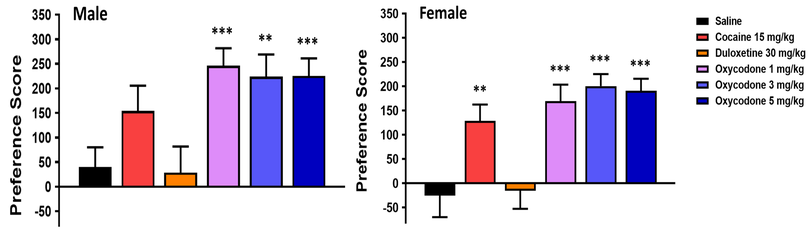
Study 2: Conditioned Place Preference

Percent time in drug-paired compartment:



*Percent time in the drug-paired compartment on Day 10 (bias test). The dot line represented 50% chance level. (**: P<0.01 and ***: P<0.001. One-way ANOVA followed by Dunnett test with saline group as reference.)*

Δ Preference score:



*The Δ Preference Score is defined as the difference of time in the compound-paired compartment between Day 1 and Day 10. This index indicates conditioning that develops during training. (**: P<0.01 and ***: P<0.001. One-way ANOVA followed by Dunnett test with saline group as reference)*

Summary

- Both male and female rats showed significant oxycodone abuse in self-administration (SA) and conditioned place preference (CPP) tests.
- The optimal dose range in the self administration test was 0.03 - 0.06 mg/kg/infusion for male rats, and 0.06 - 0.1 mg/kg/infusion for female rats.
- In the progressive ratio (PR) schedule of self-administration test, similar sex difference was found, i.e., female rats showed significantly higher breakpoint than male rats at 0.06 and 0.1 mg/kg/infusion.
- In the conditioned place preference (CPP) study, oxycodone 1, 3 and 5 mg/kg all showed significant abuse potential in both male and female rats. The three doses were almost equally effective.
- Oxycodone showed extremely strong CPP, relative to cocaine or other abused compounds we had tested before.
- This study successfully validated the abuse liability of oxycodone using two different assay in rats. Furthermore, the results of these studies confirmed the validity of both assays for studying the potential abuse liability of novel compounds in rodents.

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