Evaluation of the abuse liability of gabapentin and duloxetine 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 gabapentin and duloxetine 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 was used for both sexes. 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 that had been trained to self-administer food pellets were allowed to self-administer saline or vehicle (6% DMSO for duloxetine) (negative control), oxycodone (0.06 mg/kg/infusion (positive control), gabapentin (0.3, 1, and 3 mg/kg/infusion) or duloxetine (0.3, 1, and 3 mg/kg/infusion) by pressing the active lever on a fixed ratio 3 (FR3) schedule for 1 hour/day. Acquisition training lasted 20 days.

Study 2: Conditioned place preference (CPP):

In the CPP study, an independent group design was used with five treatment groups for both sexes. Saline or vehicle (negative control) and oxycodone 3 mg/kg (positive control) were injected intraperitoneally; gabapentin 3, 10 and 30 mg/kg or duloxetine 10, 30 and 100 mg/kg were dosed orally. 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 or vehicle on days 2, 4, 6 and 8, and with either oxycodone or test compounds on days 3, 5, 7, 9. Animals were confined in the "drug compartment" or "saline/vehicle compartment" immediately after drug administration (or 60 minutes after administration of gabapentin) 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.

Two indexes are used to represent conditioned place preference. The first is the percent of time the rats spent in the drug-paired compartment on Day 10 (at post-conditioning bias test); the second index is the Δ Preference Score, which is defined as the difference of time (seconds) in the drug-paired compartment between Day 1 and Day 10 (D10-D1). This index is the indication that conditioning has developed during the training procedure.

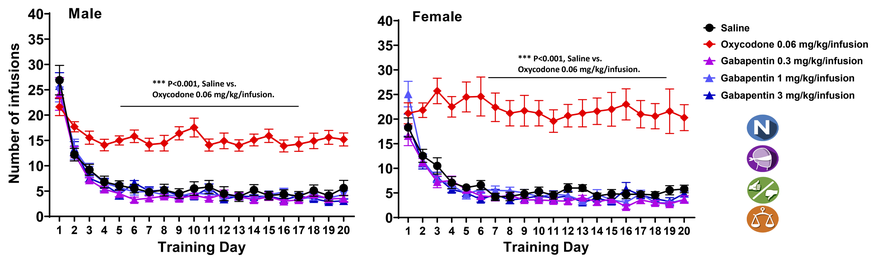
Rigor

- Sample size was determined based on power analysis.
- Experimenters were blinded to treatments.
- Inclusion/exclusion criteria were applied.
- Groups were balanced by proper baseline responses.

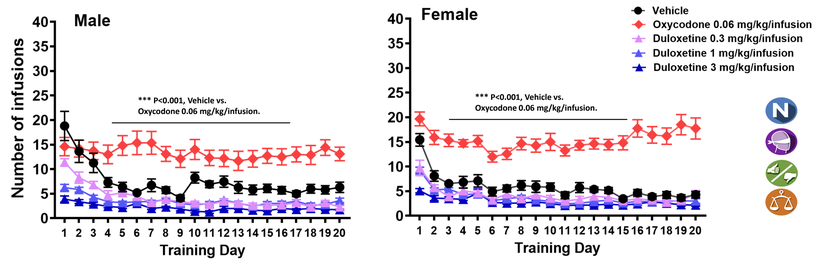
Statistical analysis:

Data were analyzed by analysis of variance and Dunnett's *post hoc* test where appropriate. Effects showing *p<0.05 were considered to be statistically significant. For self-administration experiments, ANOVAs were performed on data from Days 5-20.

Study 1: Intravenous Self-Administration



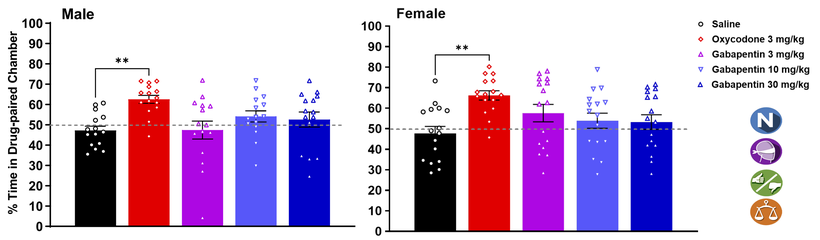
Gabapentin self-administration: Oxycodone (0.06 mg/kg/infusion) showed significant abuse liability. Gabapentin (0.3, 1 and 3 mg/kg/infusion) showed no significant self-administration when compared to saline in either male or female rats. (N=10-12 for male rats; N=10-12 for female rats)



Duloxetine self-administration: In male rats, oxycodone (0.06 mg/kg/infusion) showed significant abuse liability. Duloxetine groups (especially 3 mg/kg/infusion group) had significantly lower infusion rate than the vehicle (6% DSMO) group. In female rats, oxycodone (0.06 mg/kg/infusion) showed significant abuse liability. Duloxetine 3 mg/kg/infusion group showed significantly lower infusion rate. These data suggested that duloxetine might induce aversion. (N=11 for male rats; N=12 for female rats)

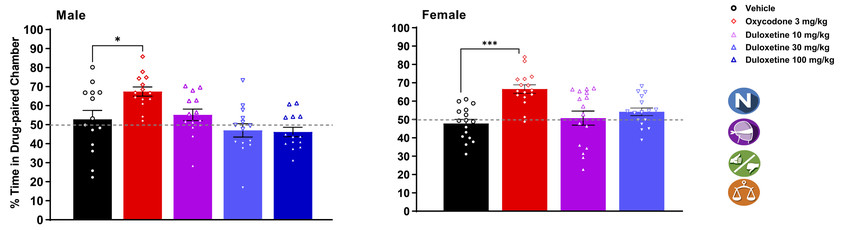
Study 2: Conditioned Place Preference

Percent time in drug-paired compartment:



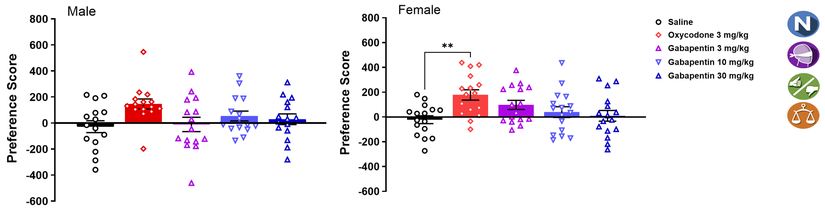
Gabapentin (3, 10 and 30 mg/kg) CPP in male and female rats, percent time in drug-paired compartment: Oxycodone (3 mg/kg) showed significant CPP. None of the doses of gabapentin caused CPP in either male or female rats. (N=15 for male rats; N=16 for female rats) (** Ps<0.01 relative to Saline group. Dunnett's *post hoc* test after significance of one-way ANOVA with all groups.)

Percent time in drug-paired compartment:



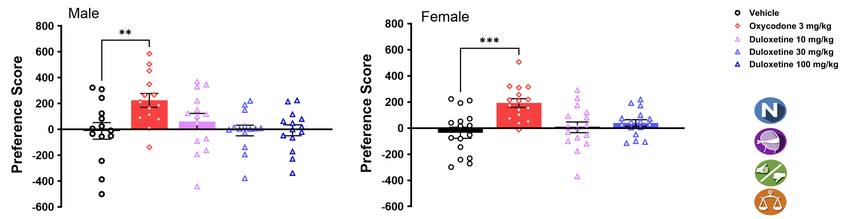
Duloxetine (10, 30 and 100mg/kg) CPP in male and female rats, percent time in drug-paired compartment: Oxycodone (3 mg/kg) showed significant CPP. None of the doses of duloxetine showed CPP in either male or female rats. Duloxetine 100 mg/kg was not well tolerated in female rats, therefore only 10 and 30 mg/kg were tested. (N=14 for male rats; N=16 for female rats) (* P<0.05 and *** P<0.001 relative to Vehicle group. Dunnett's *post hoc* test after significance of one-way ANOVA with all groups.)

Δ Preference score:



Gabapentin (3, 10 and 30 mg/kg) CPP in male and female rats, Δ Preference score: Oxycodone (3 mg/kg) showed significant CPP in female rats, but in male rats this index only showed trend (P<0.10). None of the doses of gabapentin caused CPP in either male or female rats. (N=15 for male rats; N=16 for female rats) (** P<0.01 relative to Saline group. Dunnett's *post hoc* test after significance of one-way ANOVA with all groups.)

Δ Preference score:



Duloxetine (10, 30 and 100mg/kg) CPP in male and female rats, Δ Preference score: Oxycodone (3 mg/kg) showed significant CPP. None of the doses of duloxetine showed CPP in either male or female rats. Duloxetine 100 mg/kg was not well tolerated in female rats and therefore only 10 and 30 mg/kg were tested. (N=15 for male rats; N=16 for female rats) (** P<0.01 and *** P<0.001 relative to Vehicle group. Dunnett's post hoc test after significance of one-way ANOVA with all groups.)

Summary

- Both male and female rats showed significant oxycodone abuse in self-administration (SA) and conditioned place preference (CPP) tests, confirming the validity of these two behavioral assays.
- Neither gabapentin nor duloxetine showed any sign of abuse potential in either intravenous self-administration or CPP test.
- Duloxetine (especially high dose 3 mg/kg/infusion) showed aversion in self-administration model.

This project has been funded in whole or in part with Federal funds from the National Institute of Neurological Disorders and Stroke, National Institutes of Health, Department of Health and Human Services, under Contract No. 75N95019D00026.

PSPP is currently accepting assets for evaluation

For eligibility and participation inquiries, contact:

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For more information about PSPP:

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