

2024 Virtual Conference

New Insights from Animal Models in Xylazine/Fentanyl Use

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Background

- **XYL toxicity** (Ruiz-Colón 2014, Papudesi 2023)
 - Respiratory depression (more severe in combination w/ FENT)
 - **Sedation (more severe in combination w/ FENT)**
 - **Bradycardia/hypotension**
 - **Hyperglycemia**
 - **Hypothermia**
- **Chronic exposure:**
 - **Skin ulcers**
- **Necessity for XYL reversal agent?**
 - 2023 NIDA Clinical Trials Network meeting writeup suggested agent not necessary (Perrone 2024), but decision appeared to be based on retrospective Love 2023 study.

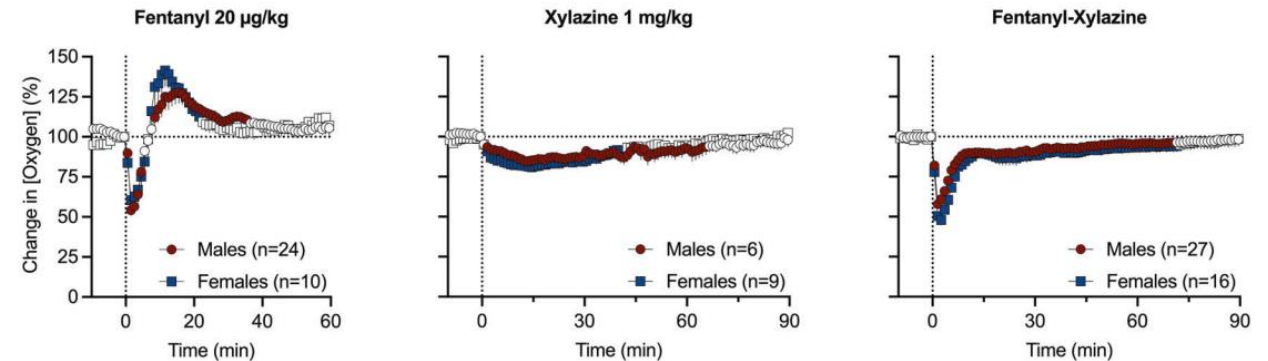
Background

- **Contribution of XYL to FENT toxicity (clinical studies)**
 - **Love 2023:** less cardiac arrest/coma WITH XYL
 - ❖ Limitations: qualitative xylazine determination (retrospective chart design), pre-hospital cardiac arrest/coma not measured, exclusively urban population
 - **Hays 2024:** higher FENT concentrations in XYL co-exposed patients
 - **German 2024:** 3x more overdose incidence and 2x more naloxone (NLX) use with presumed FENT-XYL vs FENT exposure
 - ❖ Determined FENT-XYL exposure by asking if administered XYL adulterated FENT, had a “heavy nod” > 20 min, or had “extreme dry mouth”
 - **Tan 2024:** Greater incidence of polysubstance use, overdose history, and Hepatitis C w/ XYL-FENT vs FENT
 - **Jiang 2024:** Greater incidence of non-fatal overdose with self-reported FENT-XYL vs FENT use
- **Potential pharmacotherapy: naloxone (NLX) + adjunctive atipamezole (ATI)**
 - ATI: potent $\alpha 2$ antagonist (**reverses effects of XYL**)
 - ❖ Has been shown to safely reverse the sedation, hypotension, and bradycardia resulting from dexmedetomidine (potent clinically used $\alpha 2$ agonist sedative) in humans

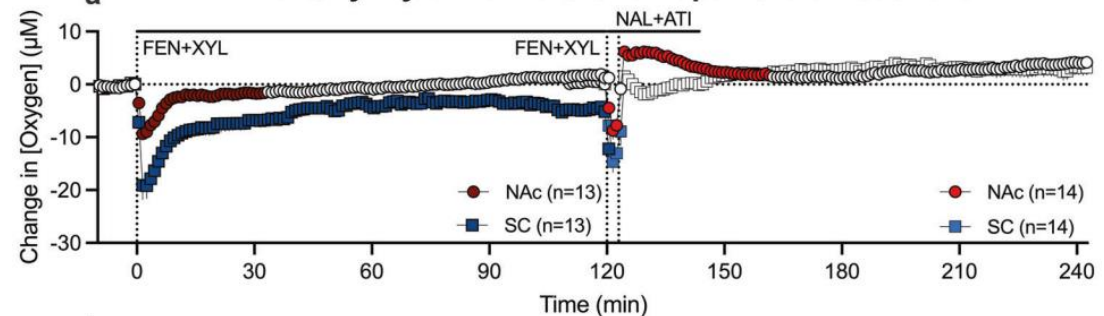
Background – FENT-XYL Respiratory Depression

- Atipamezole (ATI) + NLX for combination FENT-XYL exposure
 - Choi 2024: reversed respiratory depression in rats
 - 0.02 mg/kg FENT + 1 mg/kg XYL → 0.2 mg/kg NLX + 0.25 mg/kg ATI

A. NAc Oxygen Response



a A. Fentanyl-Xylazine: Naloxone-Atipamezole Treatment



Study objectives

- **Overall: evaluation of ATI-NLX safety and efficacy in the reversal of FENT-XYL co-intoxication in rat model**
 - Study 1: Determine XYL dose needed to produce intense, but non-fatal sedation after NLX reversal of FENT
 - Study 2: Test ATI effects on reversing XYL-induced sedation, bradycardia, hyperglycemia, hypothermia, and weight loss
 - Study 3: Evaluate the safety of ATI administration in concurrent FENT-XYL-methamphetamine (METH) exposure (i.e., if intervention enhances METH-induced agitation)

Experimental Design/Methods

- **Study 1: Determine XYL dose needed to produce intense, but non-fatal sedation after NLX reversal of FENT**
 - 0 – 20 mg/kg XYL \pm 0.1 mg/kg FENT (n = 4 male rats / group x 2)
 - 15 min later administer 0.1 mg/kg NLX
 - Perform rat coma scale assay every 5 min from 0 – 40 min

Rat Coma Scale

- Simplified, higher throughput adaptation of the method validated by Pais-Roldan (2019)
 - Note: cited method based on the human Glasgow Coma Scale, the FOUR Score, and the Coma Recovery Scale-Revised

1) WHISKER RESPONSE

- SCORE 1: Spontaneous movements
- SCORE 0: No movements

2) MOTOR FUNCTION

- SCORE 4: Walks voluntarily
- SCORE 3: Walks or withdraws upon touch to the hind paw
- SCORE 2: Walks or withdraws paw due to paw pinch
- SCORE 1: Muscle contractions due to paw pinch
- SCORE 0: No response to paw pinch

3) BRAIN STEM REFLEXES

- SCORE 2: Has both corneal and pinna reflex
- SCORE 1: One of the above reflexes present
- SCORE 0: Neither of the above reflexes present

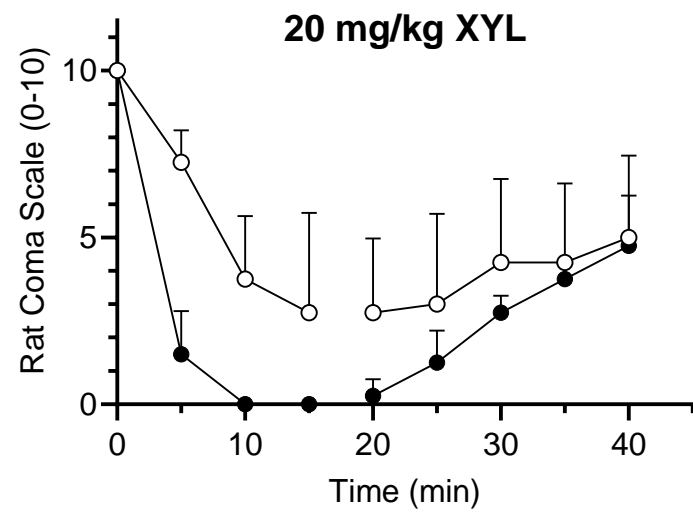
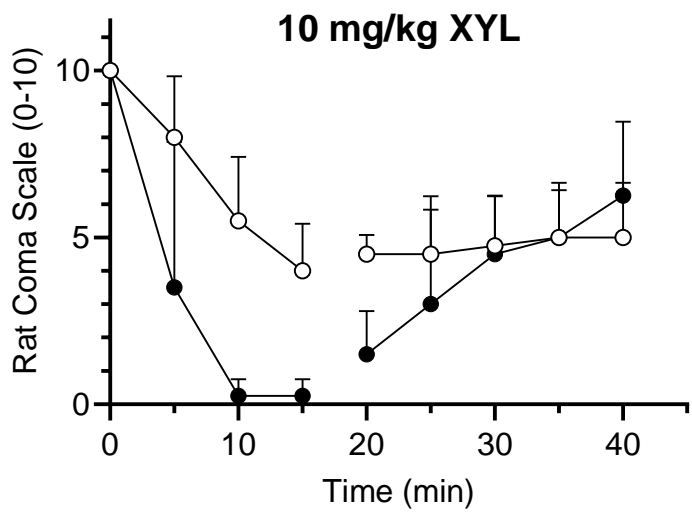
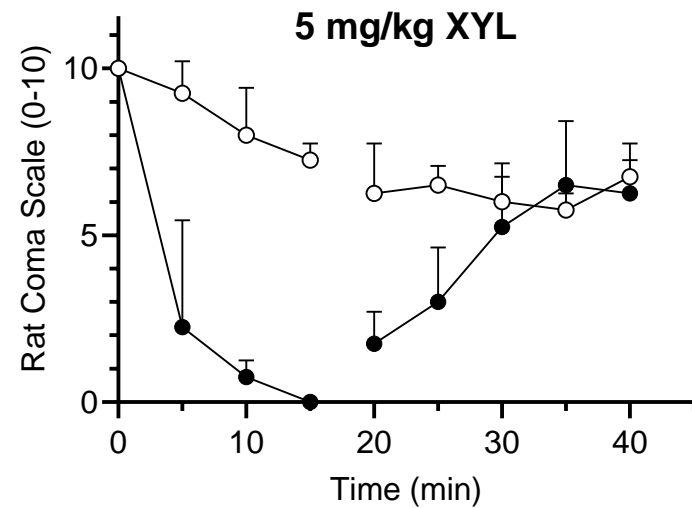
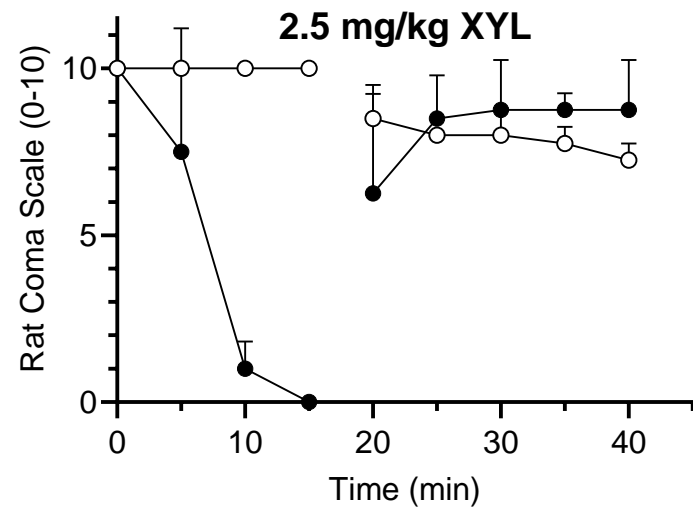
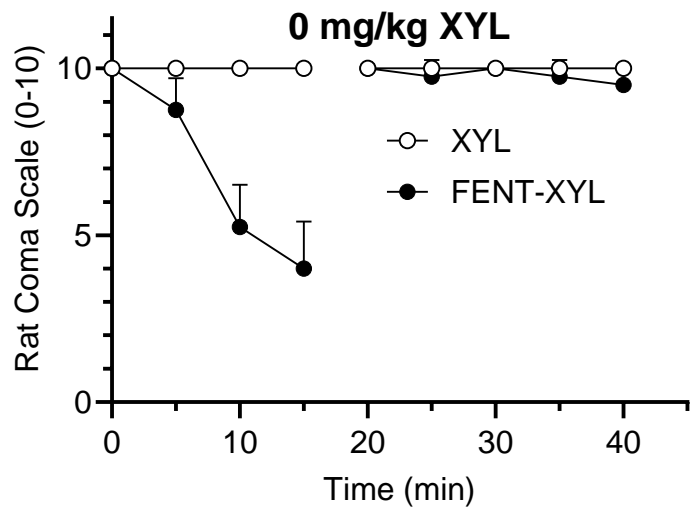
4) RIGHTING REFLEX

- SCORE 2: Normal reflex is present.
- SCORE 1: Partial (only able to right half of the body)
- SCORE 0: No reflex

5) AUDITORY RESPONSE

- SCORE 1: Auditory startle (to a clap above the head)
- SCORE 0: No response to startle

A total score is reported out of ten

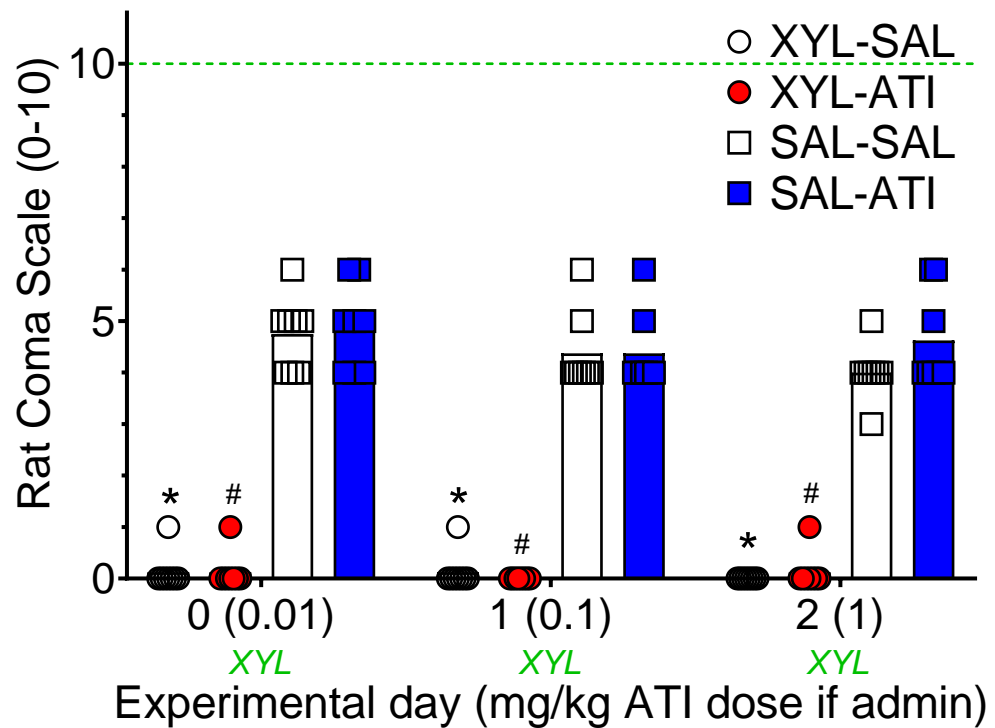


20 mg/kg XYL + 0.1 mg/kg FENT tolerably produce deep sedation which is inadequately reversed via NLX administration

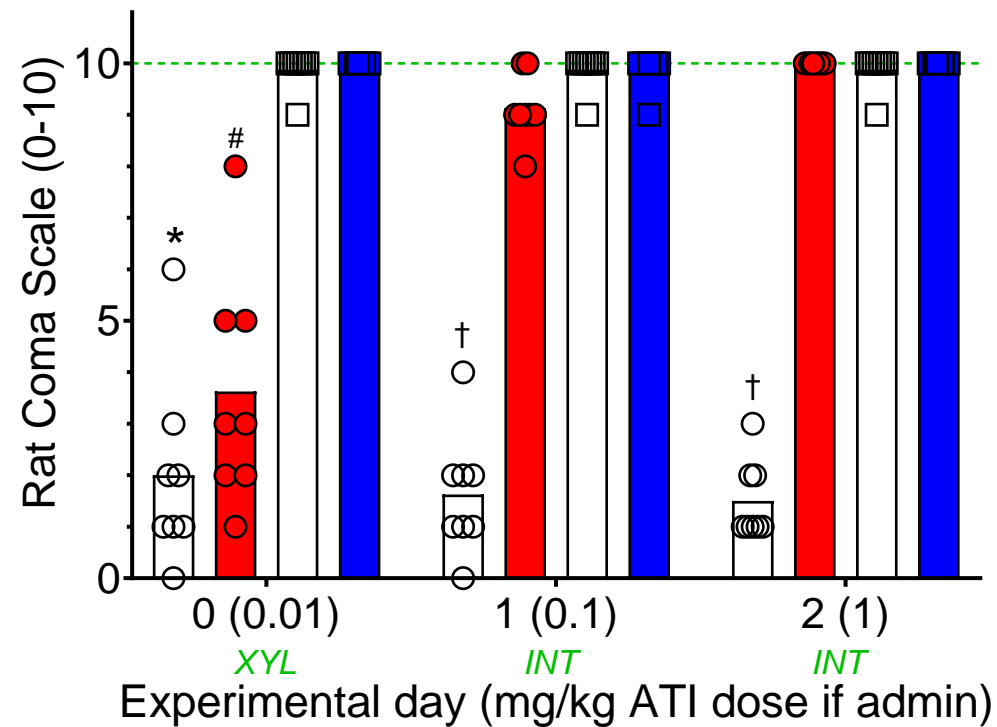
Experimental Design/Methods

- **Study 2: Test ATI effects on reversing XYL-induced sedation, bradycardia, hyperglycemia, hypothermia, and weight loss**
 - 4 drug naïve (healthy) rats to determine baseline values
 - 0.1 mg/kg FENT ± 20 mg/kg XYL (n = 8 male rats / group x 4)
 - 15 min later administer 0.1 mg/kg NLX ± ATI (0.01, 0.1, 1 mg/kg on days 0 – 2)
 - Perform rat coma scale just prior to NLX ± ATI administration and 5 minutes afterward
 - Measure heartrate (Pulse Oximeter), blood glucose (portable glucometer), temperature after coma scale measurement, and measured weight loss after 3 FENT ± XYL exposures

Pre-reversal

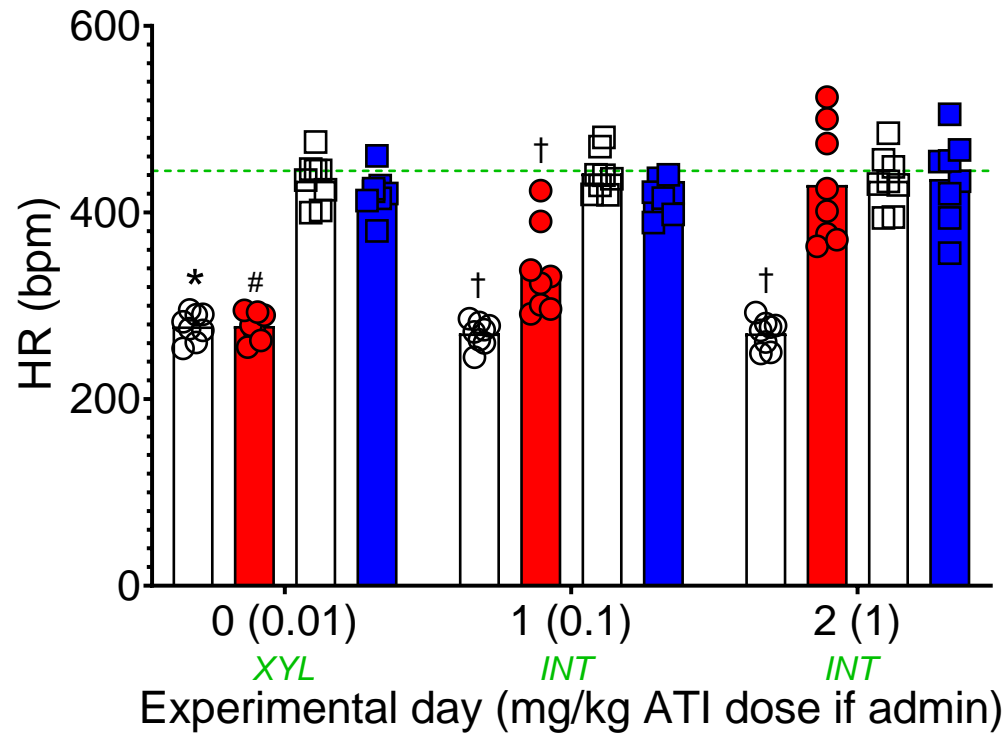


Post-reversal

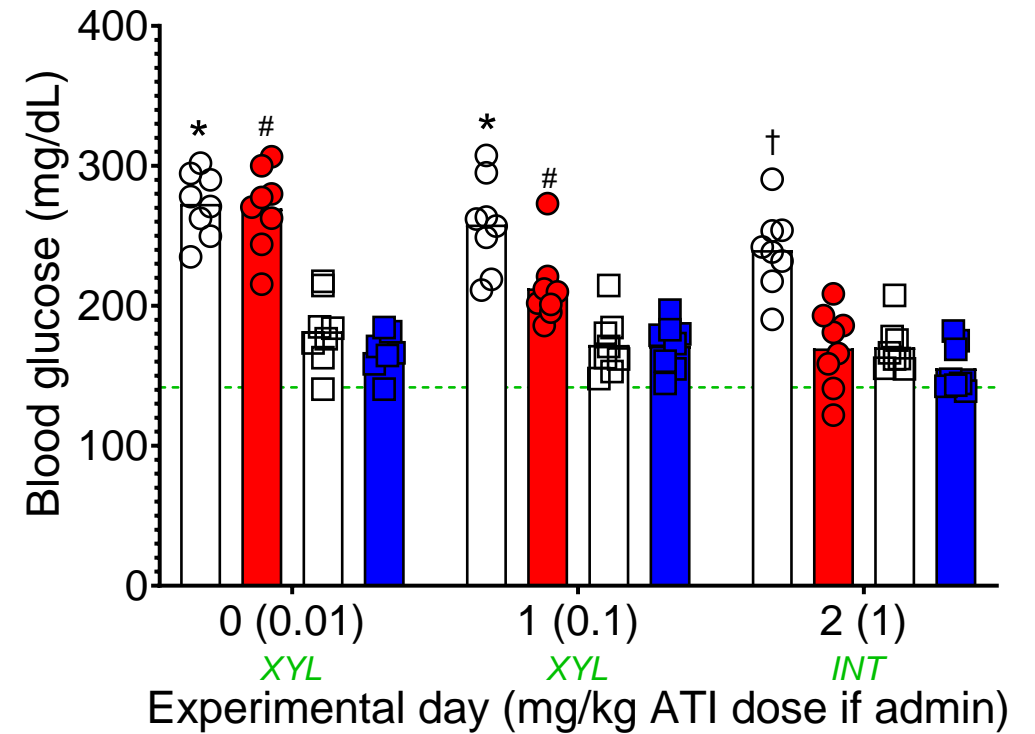


Post-reversal

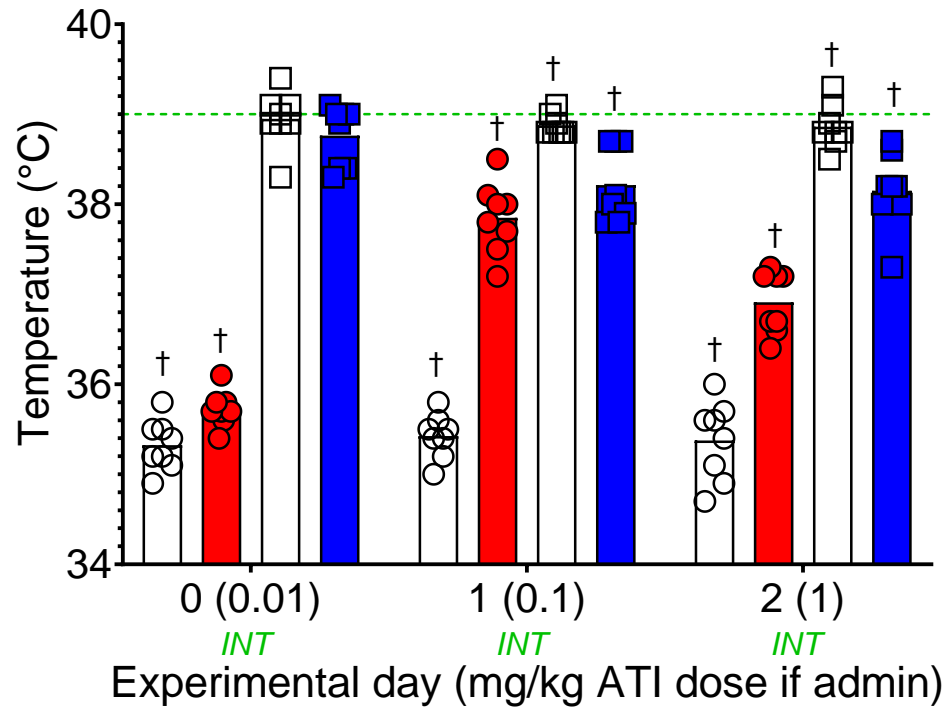
- XYL-SAL
- XYL-ATI
- SAL-SAL
- SAL-ATI



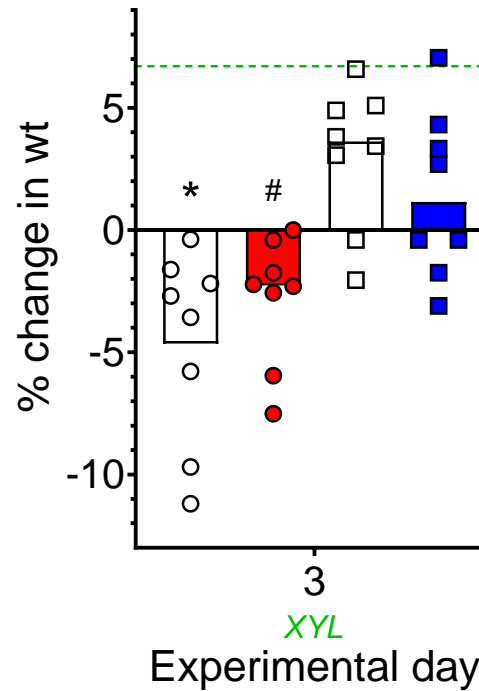
Post-reversal



Post-reversal



- XYL-SAL
- XYL-ATI
- SAL-SAL
- SAL-ATI



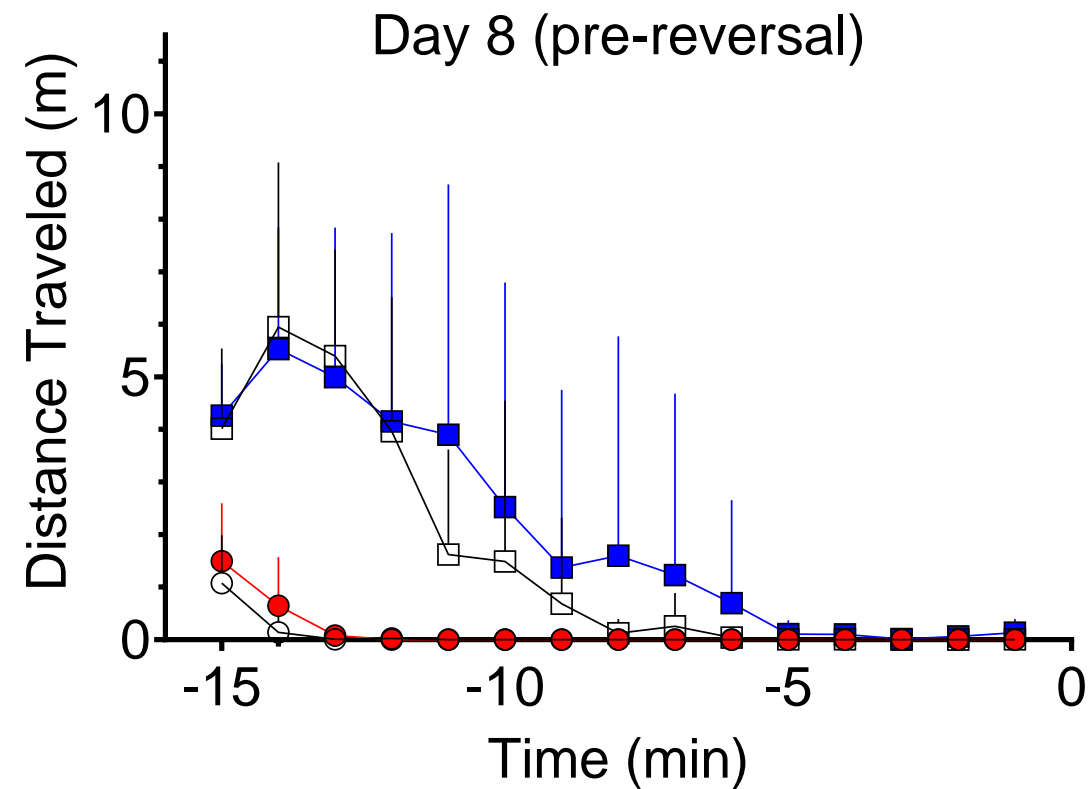
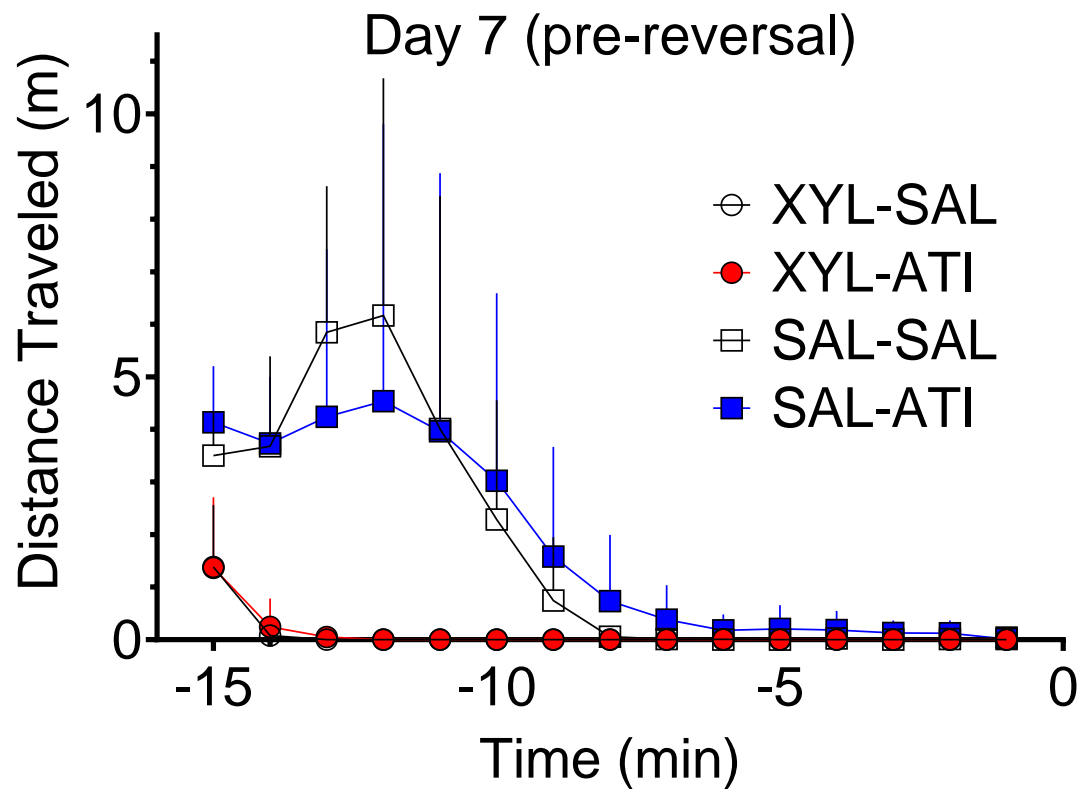
NLX-ATI most
potently reverses
FENT-XYL-induced
sedation

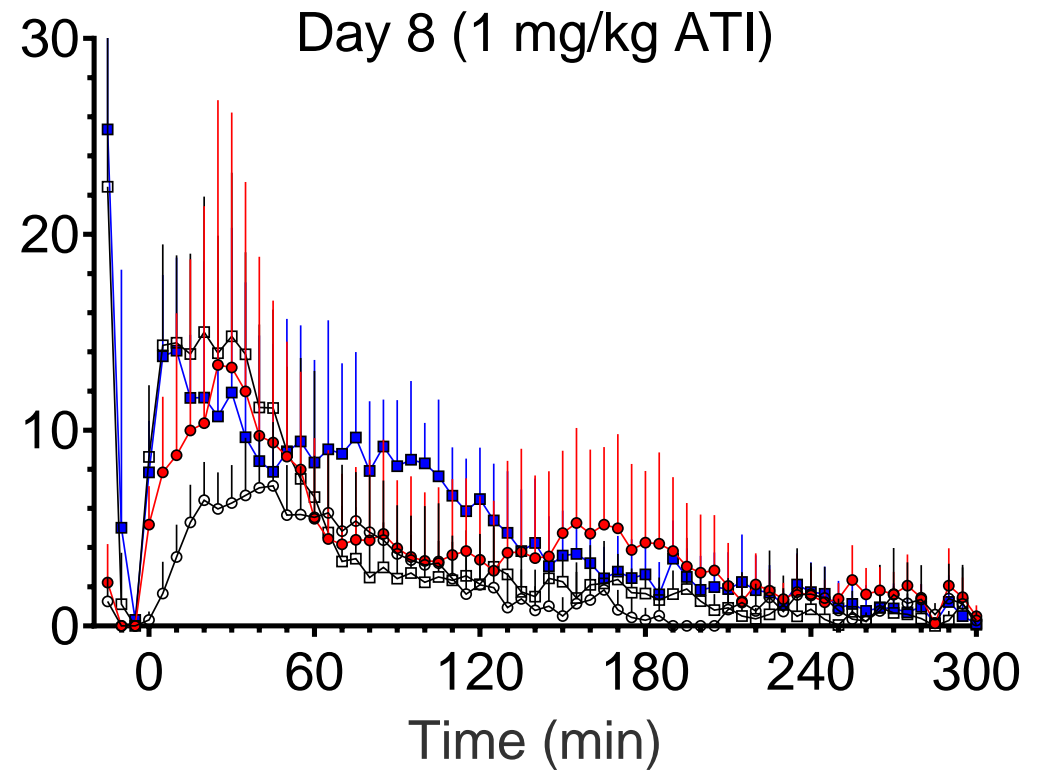
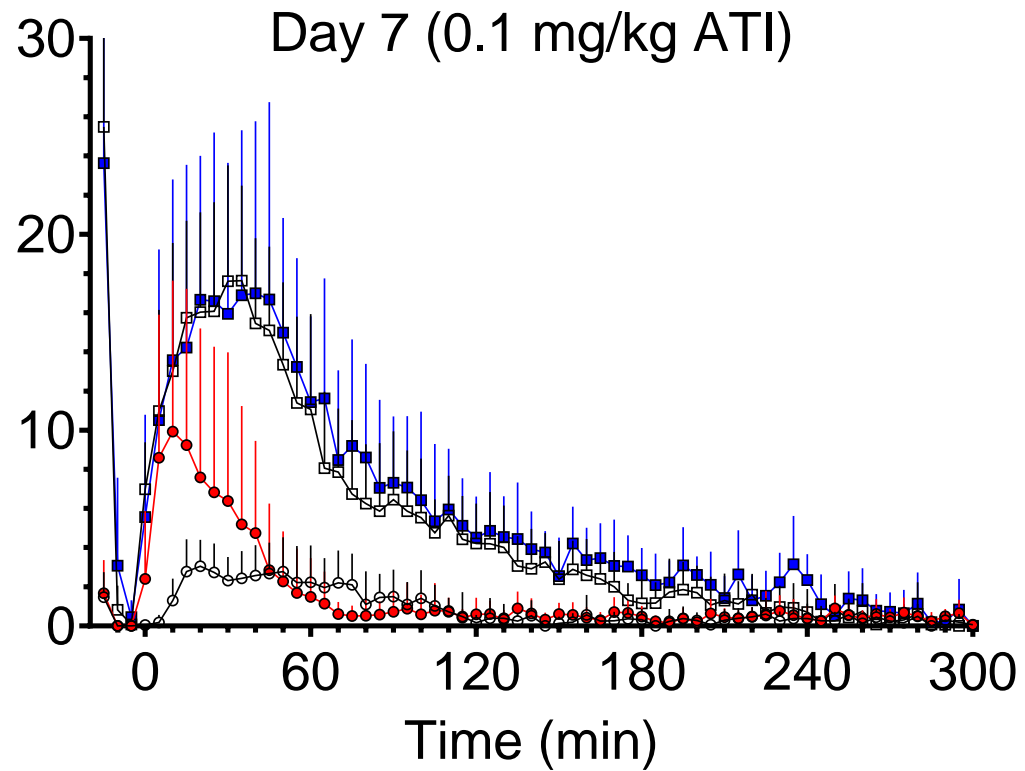
- Effective, but
less potent
reversal of
bradycardia,
hyperglycemia

Beneficial effects on
hypothermia, but
complicated by FENT-
withdrawal and effects
of ATI on TEMP

Experimental Design/Methods

- **Study 3: Evaluate the safety of ATI administration in concurrent FENT-XYL-methamphetamine (METH) exposure**
 - Rats from Study 2 (n = 8 male rats / group x 4) after 5 day washout (6 / group in current dataset, remaining 2 next week)
 - 1 mg/kg METH + 0.1 mg/kg FENT ± 20 mg/kg XYL (to evaluate FENT ± XYL on sedation in combination with METH)
 - Measure 15 min locomotor activity (Noldus Ethovision) in open field chamber – rat model of METH-induced agitation
 - Remove rat from chamber to administer 0.1 mg/kg NLX ± ATI (0.1 and 1 mg/kg on days 7 and 8)
 - Measure 300 min locomotor activity to evaluate effect of XYL and ATI on METH-induced locomotor activity (rat model of METH-induced agitation) after NLX reversal of FENT





Chronic effects of FENT-XYL exposure

- Below measurements were NOT improved by NLX-ATI treatment
 - **Day 9 skin sores** (# rats with sores)
 - ❖ XYL-SAL: 7 out of 8 (5 with inflammation)
 - ❖ XYL-ATI: 7 out of 8 (4 with inflammation)
 - ❖ SAL-SAL: 0 out of 8
 - ❖ SAL-ATI: 0 out of 8
 - **Whole blood counts**
 - ❖ Minor effect on some blood counts (neutrophils, lymphocytes, basophils)
 - ❖ May be involved in less effective healing and immune function

Summary

- NLX-ATI may be useful in reversing FENT-XYL-induced sedation, bradycardia, hyperglycemia, and to some extent hypothermia
- NLX-ATI did not prevent FENT-XYL-induced weight loss, skin sore formation, or effects on blood counts
- NLX-ATI did not enhance METH-induced locomotor activity (i.e., rat model of METH-induced agitation) when carefully dosed

Any questions?

Thank you!

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- **The healthcare professionals serving patients affected by substance use disorder in our community**