DMX-101 Does Not Exhibit Reinforcing Effects in a Hydrocodone-Trained Rat Self-Administration Model

Virginia Sanders, PhD[1]; Nikhilesh Singh, PhD[1]; Eric Strain, MD[2]

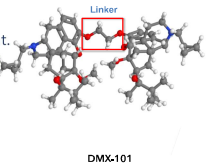
Affiliations: 1) DIMERx, Inc.; 2) Johns Hopkins University School of Medicine, Behavioral Pharmacology Research Unit

Abstract

- **Background/Aims:** Abuse liability assessment is essential for thebaine-based drug development. DMX-101 is a novel buprenorphine dimer analgesic designed to preferentially engage peripheral opioid receptors while limiting central nervous system exposure and hence decrease abuse potential. This study assessed the reinforcing effects of DMX-101 using a validated intravenous rat self-administration model with hydrocodone as a positive control.
- **Methods:** Male Sprague–Dawley rats were trained to self-administer hydrocodone (0.18 mg/kg/injection) under a fixed-ratio 10 (FR10) schedule until stable responding was achieved. Animals then completed 3-day substitution sessions with saline, vehicle, hydrocodone, or DMX-101 (0.1, 0.18, or 0.28 mg/kg/injection; n=6 each). Reinforcement was evaluated using injections per session and response patterns across test days. A Day 1 increase followed by declining responding on Days 2–3 (extinction burst) was predefined as evidence of non-reinforcement.
- **Results:** Hydrocodone consistently maintained self-administration across all test days, confirming assay sensitivity. In contrast, DMX-101 did not sustain responding beyond the initial extinction burst and showed a dose-independent progressive decline in injections across sessions. These effects occurred at exposures as high as 18-fold over the maximum feasible steady-state Cmax of ~2000 ng/mL. Prior vehicle exposure attenuated initial responding without affecting the overall extinction profile of DMX-101.
- **Conclusions:** DMX-101 did not demonstrate reinforcing effects in a hydrocodone-trained rat self-administration paradigm, even at supratherapeutic exposure multiples. Behavioral variability and vehicle history did not confound interpretation. These findings support a low likelihood of abuse potential for DMX-101 and are relevant to ongoing regulatory and clinical development of this novel analgesic.

DMX-101 Introduction

- DIMERx is developing DMX-101,a novel covalently linked dimer of buprenorphine (BPN) that targets peripheral opioid receptors without engaging the central nervous system (CNS).
- DMX-101, unlike BPN, is an orally bioavailable partial μ-opioid agonist/full κ-opioid antagonist that, does not penetrate the brain.
- Up to 60-80% of opioid receptors are peripheral, making them a precise target for pain management.
- DMX-101, which selectively acts on peripheral opioid receptors, holds promise for managing pain while avoiding the risks associated with CNS opioid receptor involvement.



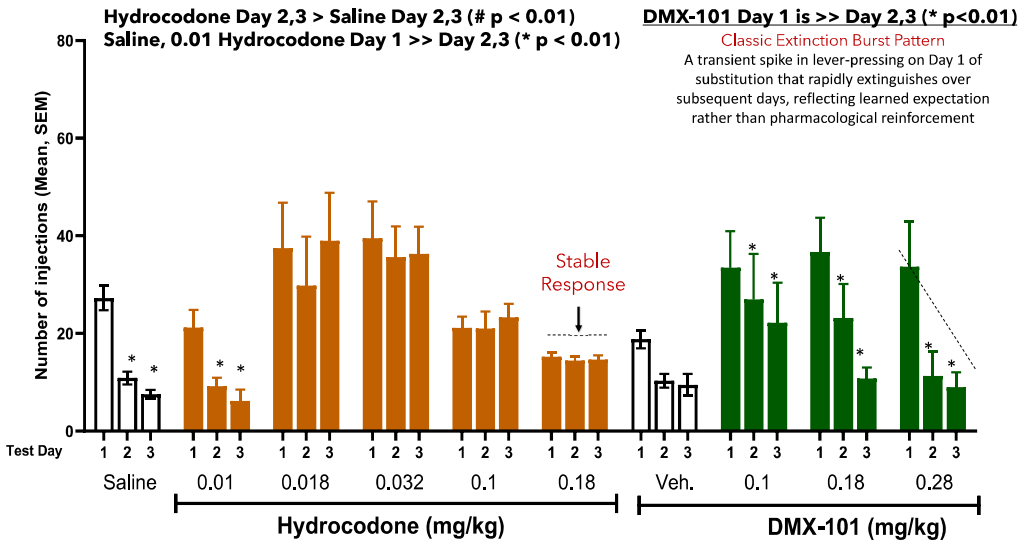
Aims and Experimental Flow

The purpose of this study was to assess the reinforcing effects of DMX-101 using a validated intravenous rat self-administration model with hydrocodone as a positive control.

Training Session		Conditioning Session		Test/Substitution Sessions
Stage 1- 7-14 days Pellet Reinforcement	Stage 2- 5-10 days Cocaine Reinforcement	Stage 3 14-21 days Hydrocodone Conditioning	Stage 4 Stable Operant Response	Stage 5 (mg/kg/injection)
Fixed Ratio (FR) = 1 lever: 1 pellet (from FR1:1 to FR 4:1	1 food pellet= 1 injection of cocaine 0.56 mg/kg/injection From FR4:1 to FR 7:1 5-7 days/week	Hydrocodone 0.18 mg/kg/injection From FR7:1 to FR10:1	≤ 20% day to day variations over 3 consecutive sessions FR10:1	I) Hydrocodone 0.18 test (n=27) II) Saline (n=27) III) Hydrocodone: 0.01,0.018,0.032, 0.10, 0.18 (n=6) IV) Vehicle (n=6) V) DMX-101 0.1, 0.18, 0.28 (n=6)

- Vehicle (pH 2.5) was introduced after all rats received hydrocodone (test and maintenance)

Fig. 1 DMX-101, unlike centrally-acting hydrocodone, does not reinforce drug-seeking behavior



Plasma Exposure Margin vs Human Cmax Steady-state

Time (min)	30	60
Ave. DMX-101 levels	25,767 ng/mL	35,733 ng/mL
	14.4x	20.0x

FDA Guidance expects >2-3x

Fig. 2- Vehicle pre-exposure attenuates initial responding across DMX-101 doses (0.28 mpk)

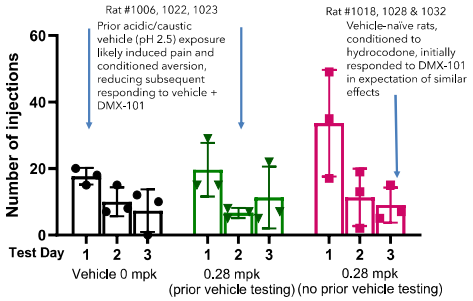
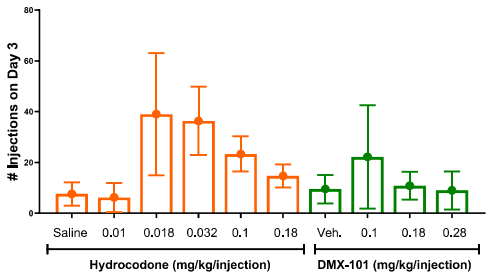


Fig. 3- Number of DMX-101 injections on Day 3 are similar to vehicle on same day



Conclusions: DMX-101 does not serve as a reinforcer in rats conditioned to self-administer hydrocodone

- DMX-101 exhibited a classic extinction burst pattern, a recognized indicator of non-reinforcement, even at exposures 18X highest steady state Cmax in humans
  - Declining injections over 3 days showed a "downward staircase" pattern—recognized as a biomarker of ineffective reinforcement
  - DMX-101 showed no difference from vehicle treated controls andoverall responses comparable to saline
- The self-administration study, consistent with prior data, further de-risks DMX-101 by supporting its non-abuse profile
  - Prior observations: lack of any signals in the rat Irwin test, locomotor study, PK analysis, lack of withdrawal symptoms in repeat-dose preclinical studies, lack of opioid-like adverse events in Phase 1 and Phase 2 clinical trials

Acknowledgements:
Funded by: NIH Grant UG3DA 061645-01A1
Study conducted at Charles River, Mattawan

NIH HEAL INITIATIVE

DIMERx