Neuropharmacodynamic Profile of NKTR-181: Correlation to Low Abuse Potential

Laurie VanderVeen, Takahiro Miyazaki, Irene Choi, Michael A. Eldon, Xue Snow Ge, Hema Gursahani, Faye Hsieh, Aleksandrs Odinecs, Jonathan Zalevsky, and Stephen K. Doberstein

Nektar Therapeutics, San Francisco, CA

Disclosures

- LV, TM, IC, ME, XG, HG, FH, AO, JZ, and SD are current or former employees of Nektar Therapeutics

Characteristics of Drugs of Abuse

- Shorter intervals between drug intake and perceived effect (euphoric "high") correlate with greater abuse potential
- Fast rate of drug uptake into brain
- Rapid activation of dopamine reward circuits in the brain
  - Rapid dopamine release in the striatum is associated with euphoria
  - Speed of dopamine release and the magnitude of effect is directly linked to the likelihood that a drug will be abused
- An opioid that avoids these characteristics is expected to have less abuse potential than conventional opioids

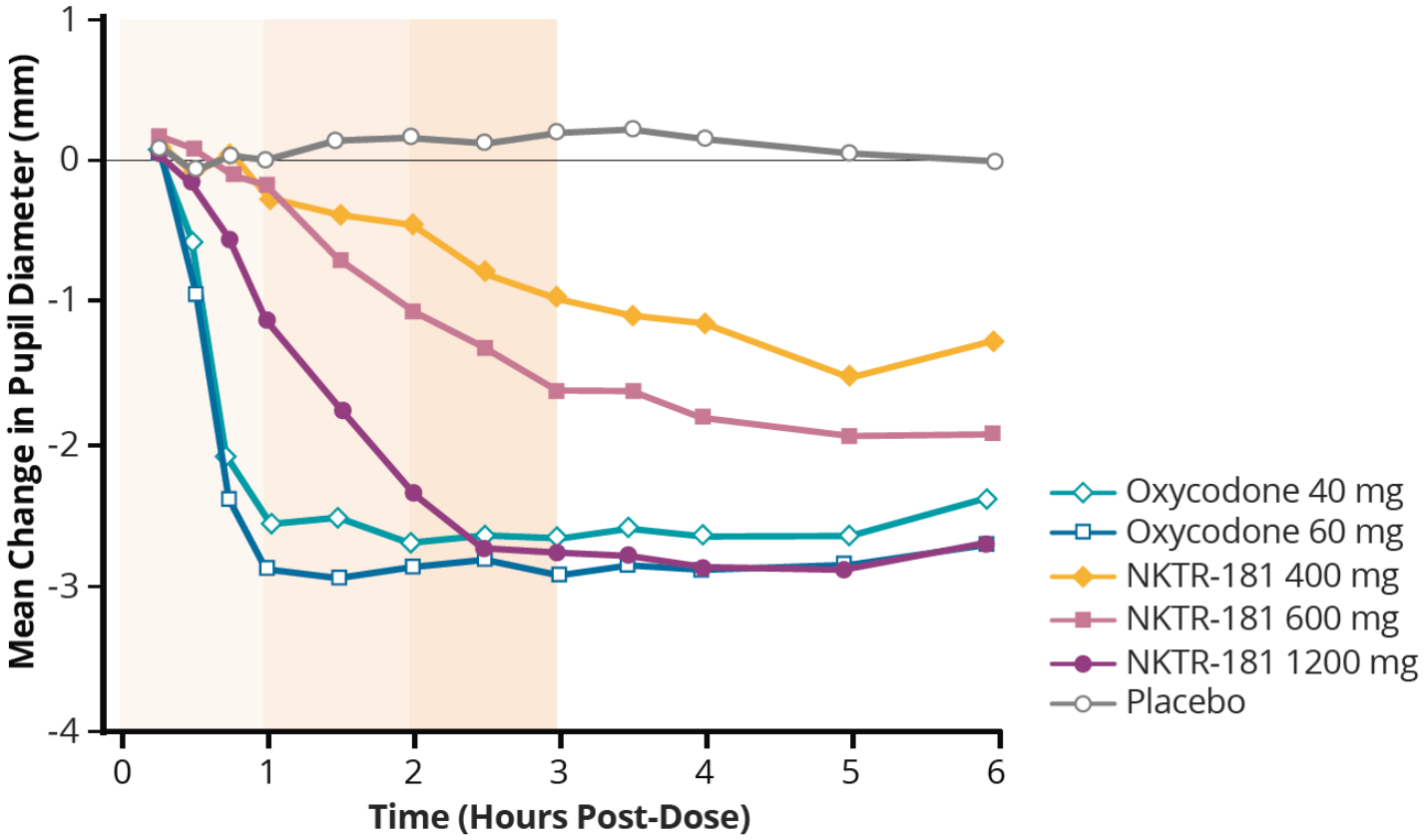
Oldendorf W. *NIDA Res Monogr* 1992;120:13-25
Volkow and Morales *Cell* 2015;162:712-725

NKTR-181: A Novel Opioid for Treatment of Chronic Pain

- New molecular entity, full mu-opioid receptor agonist designed to have slow rate of entry into the brain relative to conventional opioids[1]
  - Slow CNS entry rate dependent on unique physicochemical properties that are inherent to the NKTR-181 molecule
  - No known chemical or physical methods to alter NKTR-181 to increase its CNS entry rate
- Significant, clinically meaningful analgesia in phase 3 clinical trial in patients with moderate-to-severe chronic low back pain[2]
- Significantly lower mean peak Drug Liking scores at therapeutic doses relative to oxycodone in human abuse potential studies[3]
  - Poster 36: Henningfield et al. Thursday 12-2 pm
- Low abuse potential in preclinical models[1]

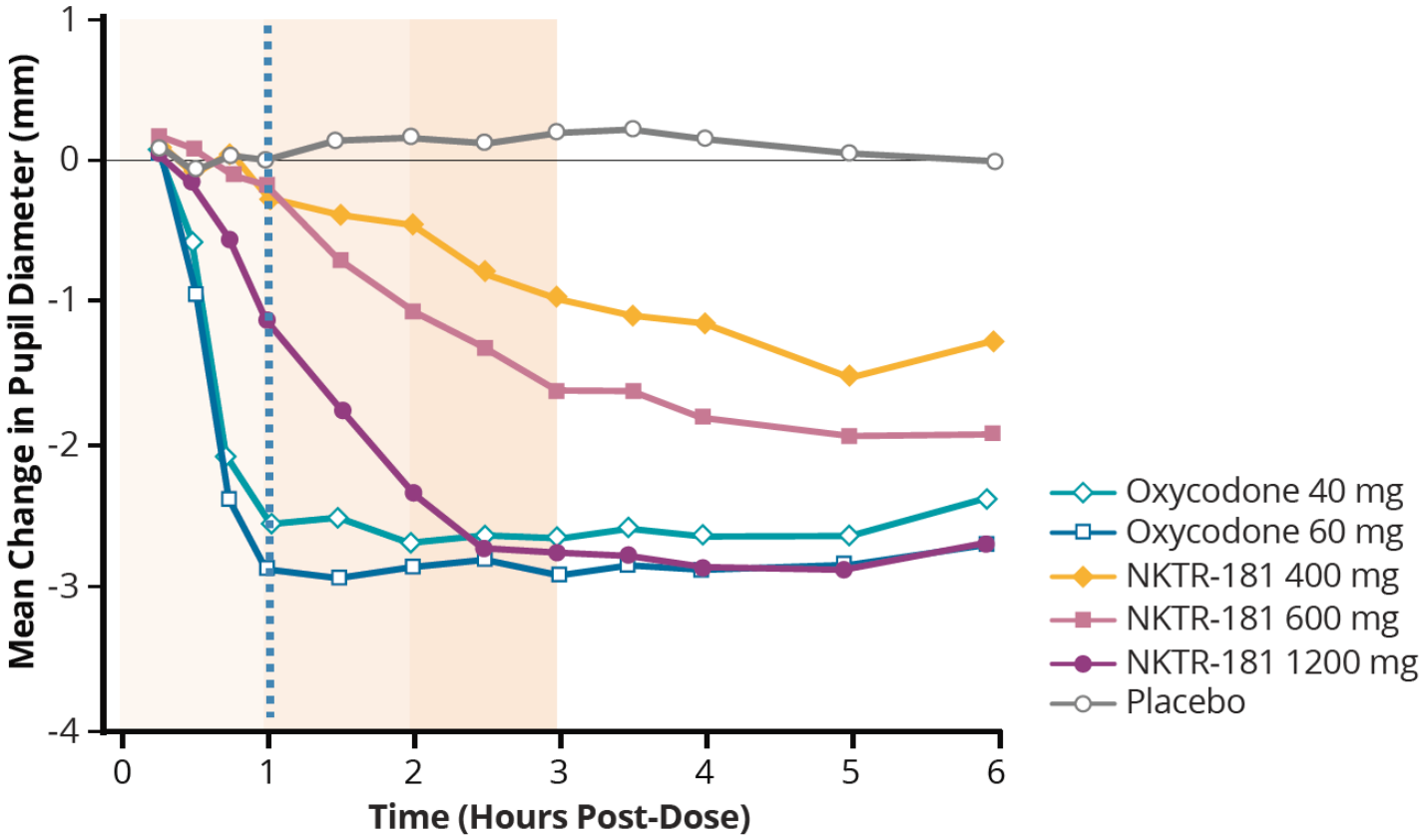
1. Miyazaki T, et al. *J Pharmacol Exp Ther* 2017;363:104-113.
2. Markman, J, et al. *Postgrad Med* 2017;129(suppl1):28-29.
3. Webster L, et al. *Pain Med* 2018;19:307-318.

Time Course of Pupil Constriction Delayed Relative to Oxycodone in Human Subjects



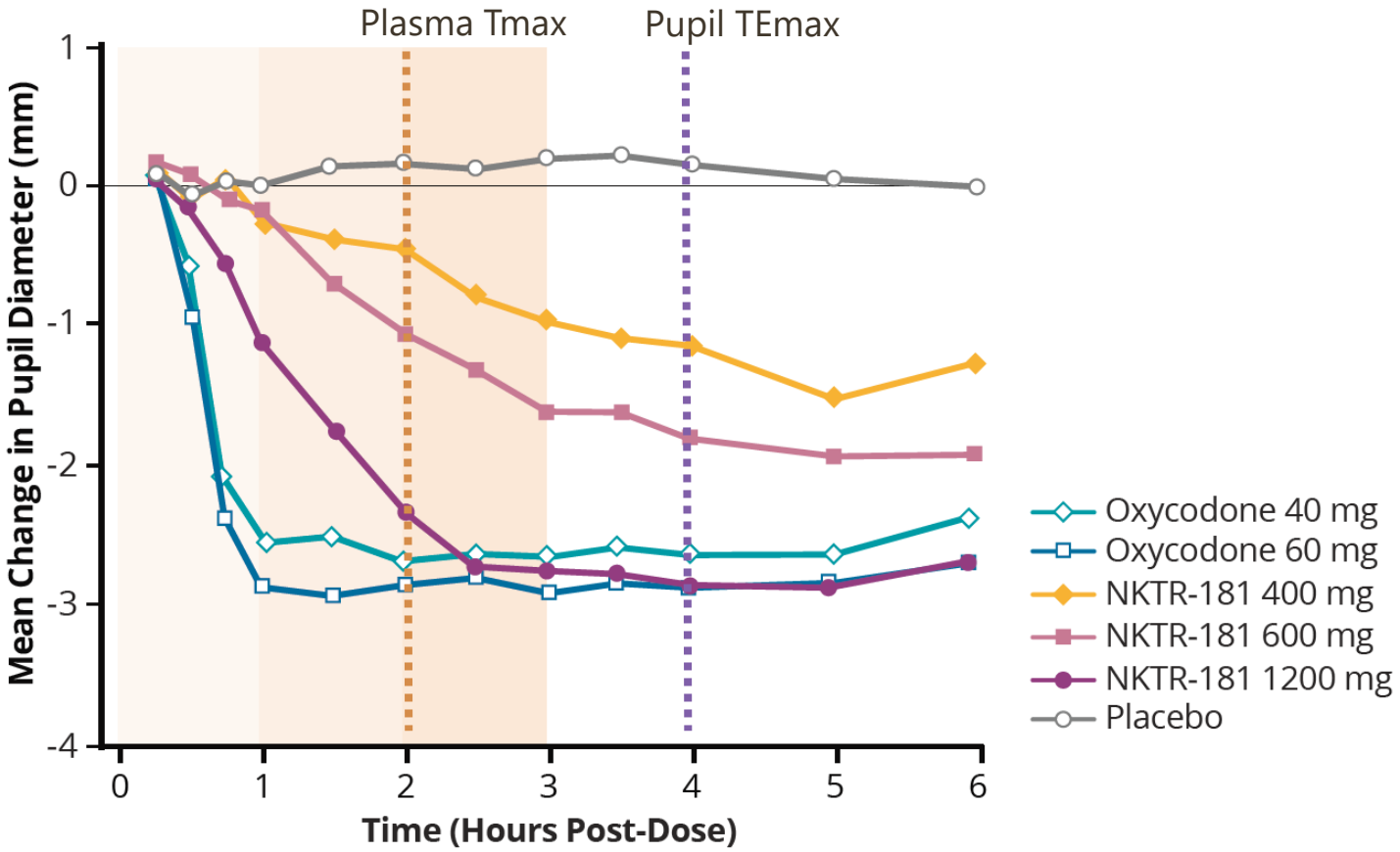
Double-blind, randomized, placebo-controlled, single-dose crossover study in recreational opioid users

Similar Time Course of Peak Pupil Constriction and Peak Oxycodone Plasma Concentration



- Reflects rapid distribution of oxycodone into CNS

Peak Pupil Constriction is Delayed Relative to NKTR-181 Plasma T_{max}

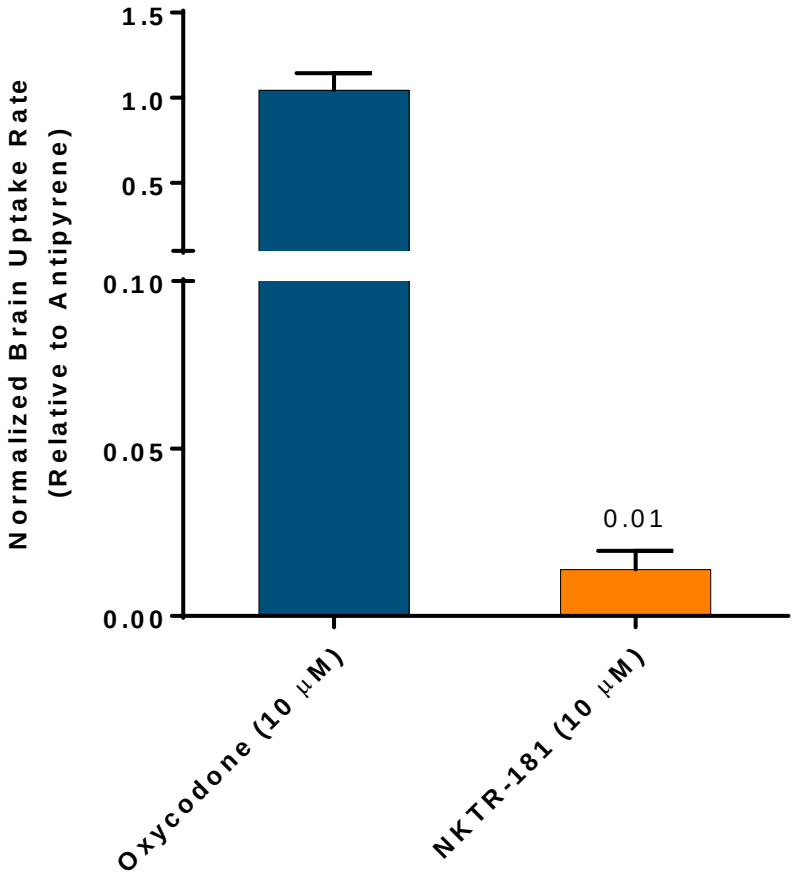


- NKTR-181 time of maximum pupil constriction observed 2-3 hours after time to peak plasma concentration, consistent with slow entry of NKTR-181 into the CNS

Objective: Characterize Components of NKTR-181 Abuse Potential MOA

- Rate of brain entry
- Mu-opioid receptor binding kinetics
- Time profile of dopamine release in nucleus accumbens

NKTR-181 Demonstrates 70-fold Slower Brain Uptake than Oxycodone in Rat



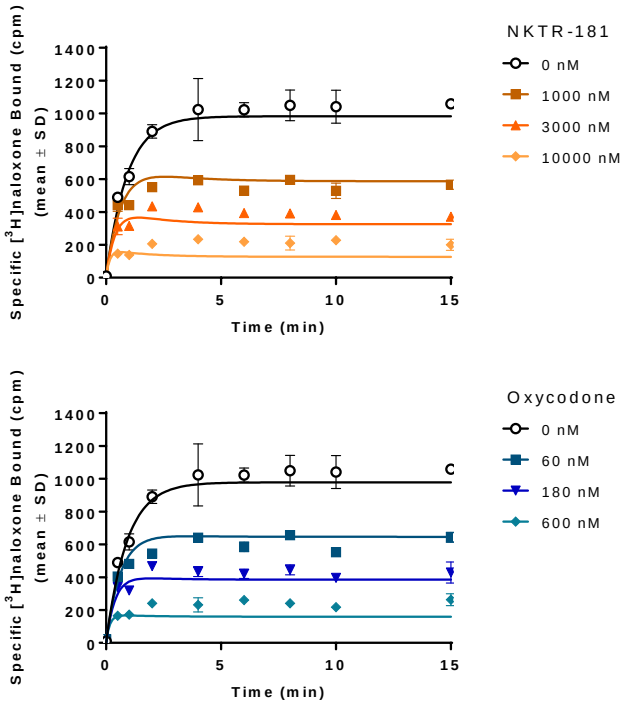
- *In situ* brain perfusion in rat
  - Single 30 second perfusion into carotid artery of anesthetized rats
  - Brain uptake rate (K_{in}) calculated from drug concentrations measured in brain at end of perfusion

Compound	$K_{in,\ perfusion}$ (mL/g/min)	
	10 μM	100 μM
Oxycodone	0.497 ± 0.121	0.560 ± 0.056
NKTR-181	0.007 ± 0.005	0.008 ± 0.005

N = 4 male Sprague-Dawley rats/group
Data are presented as mean ± SEM

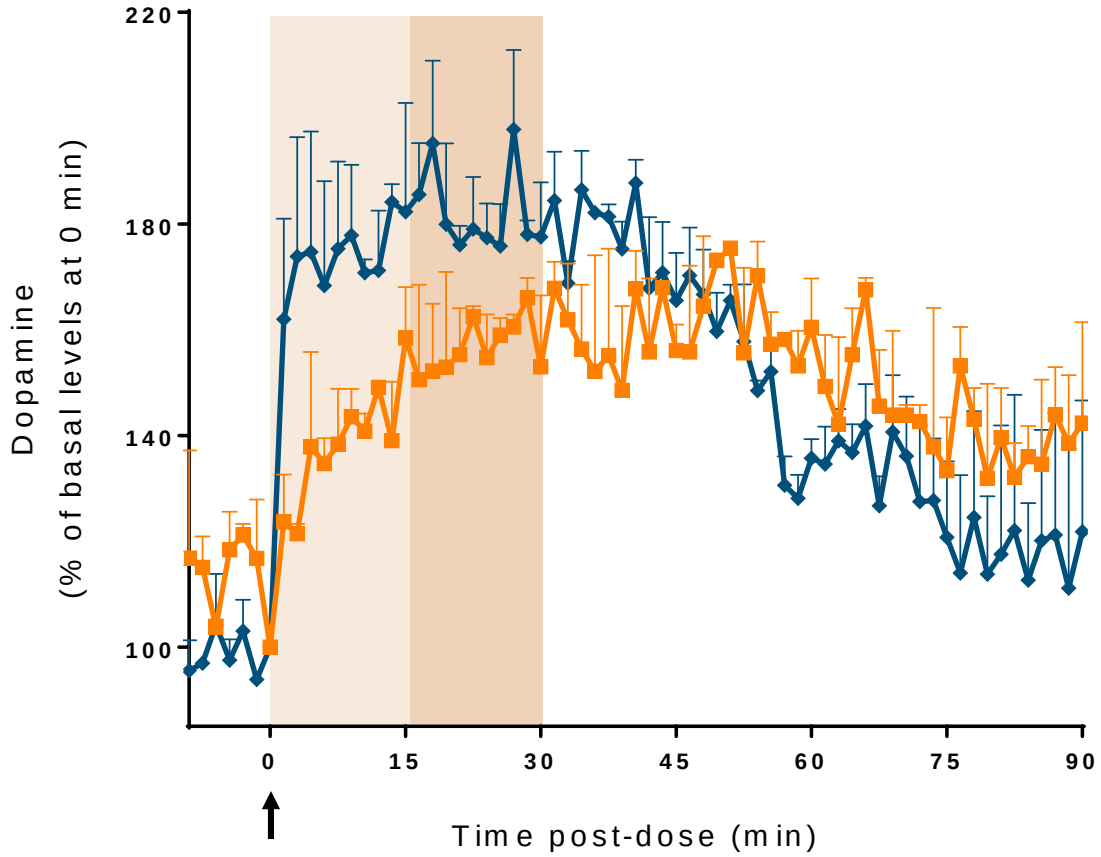
NKTR-181 Binds Mu-Opioid Receptor with Slower Association Rate and Moderate Affinity

Ligand	k_{on} ($M^{-1}min^{-1}$)	k_{off} (min^{-1})	K_d (nM)
NKTR-181	5.45 x 10^5	0.443	813
Oxycodone	8.68 x 10^6	0.554	63.8



Competition binding of [^{3}H]naloxone to hMOR in CHO-hMOR cell membrane preparations
Method of Motulsky and Mahan 1984 Mol Pharmacol 25; 1-9

NKTR-181 Induces Slower Onset of Dopamine Release in Rat Nucleus Accumbens

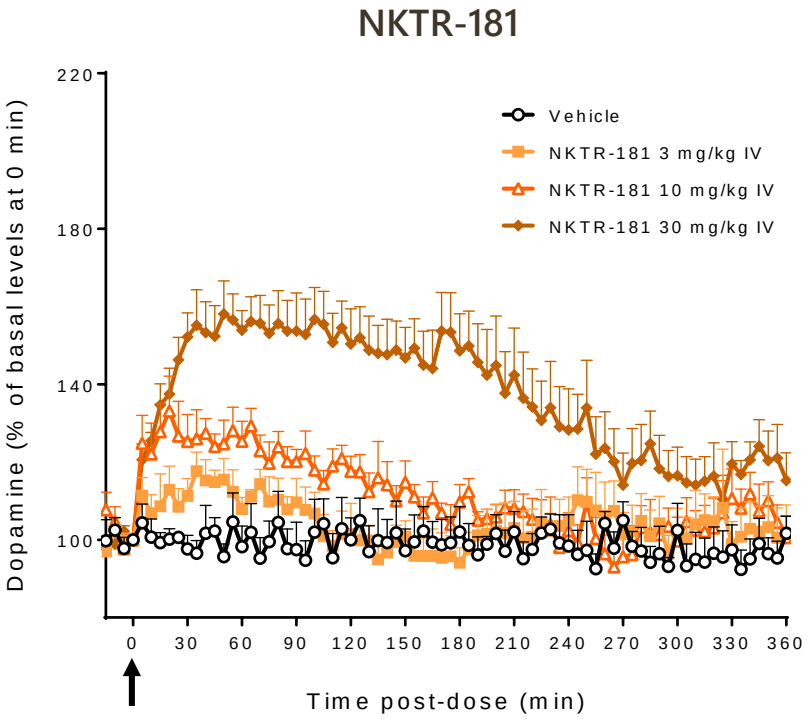


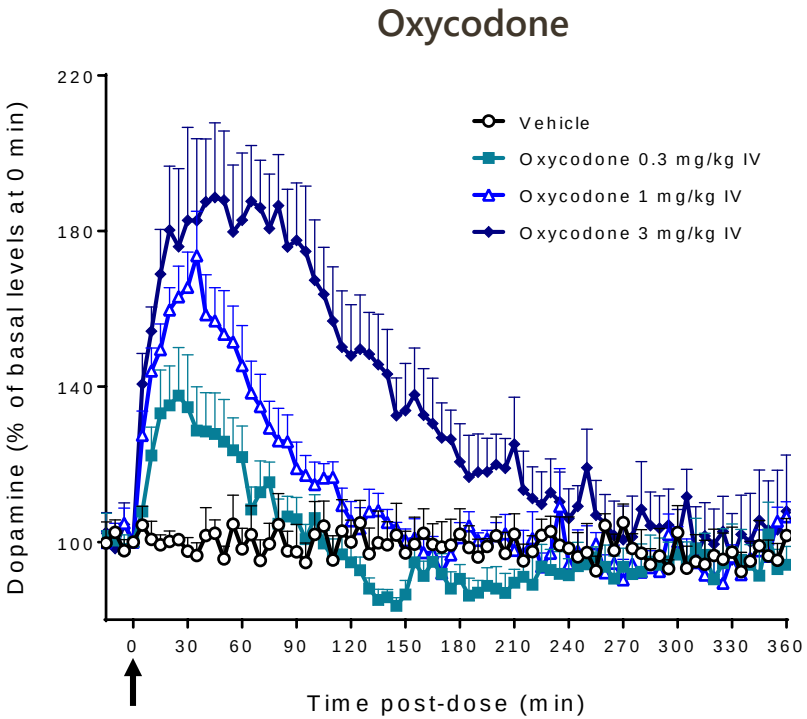
- Single intravenous dose in awake rats
- Dopamine levels measured in nucleus accumbens shell using microdialysis

N = 2-3 male Sprague-Dawley rats/group
90 second sampling interval

Differential Kinetics of Dopamine Response to NKTR-181 and Oxycodone

- Reduced magnitude of dopamine release relative to 10-fold lower dose of oxycodone
- Slower offset of dopamine effect





N = 6-7 male Sprague-Dawley rats/group
5 minute sampling interval

Conclusions

- NKTR-181 has a pharmacodynamic profile distinct from oxycodone
  - Slower rate of uptake into brain
  - Slower association with target receptor
  - Slower onset of dopamine release consistent with its slower target site distribution and receptor binding kinetics
- This unique profile supports a mechanism for the low abuse potential observed with NKTR-181