PK/PD analysis in assessment of abuse deterrence

Megan J. Shram, PhD

Director and Principal, Altreos Research Partners Inc.

Adjunct Professor and Lecturer, Department of Pharmacology, University of Toronto
INC Research Consultant

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Acknowledgments

- Consultant to pharmaceutical and biotech companies
- Thank you to Purdue Pharma, LP for permission to present data on reformulated OxyContin® and OXN

Outline

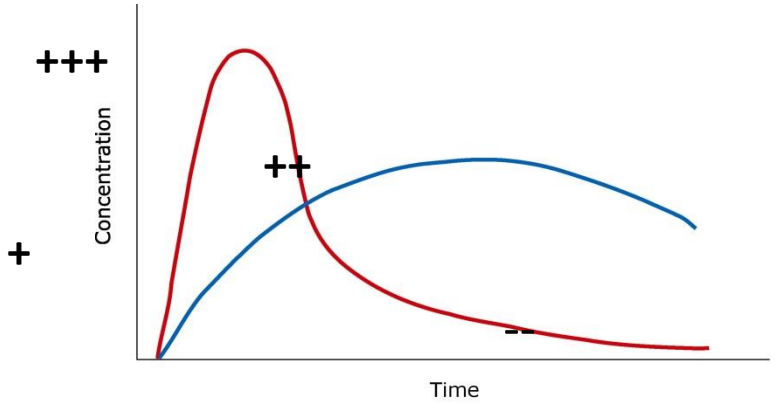
- Background on PK/PD in abuse potential
- What is PK/PD relationship of opioids?
  - Determinants of variation
- Application of PK/PD analysis in development of abuse-deterrent formulations (ADF)

Introduction

- Draft Guidance on Assessment of Abuse Potential of Drugs (January 2010):
  - "Characterization of the PK/PD properties of a…product is important for determining the abuse potential of a…product."
- Draft ADF guidance (January 2013):
  - "PK data should be collected to correlate with the PD outcomes."
  - "The rate of rise of drug onset for the intact and manipulated potentially abuse-deterrent formulation should be given appropriate weight in the overall analysis of the abuse deterrent properties."

Introduction

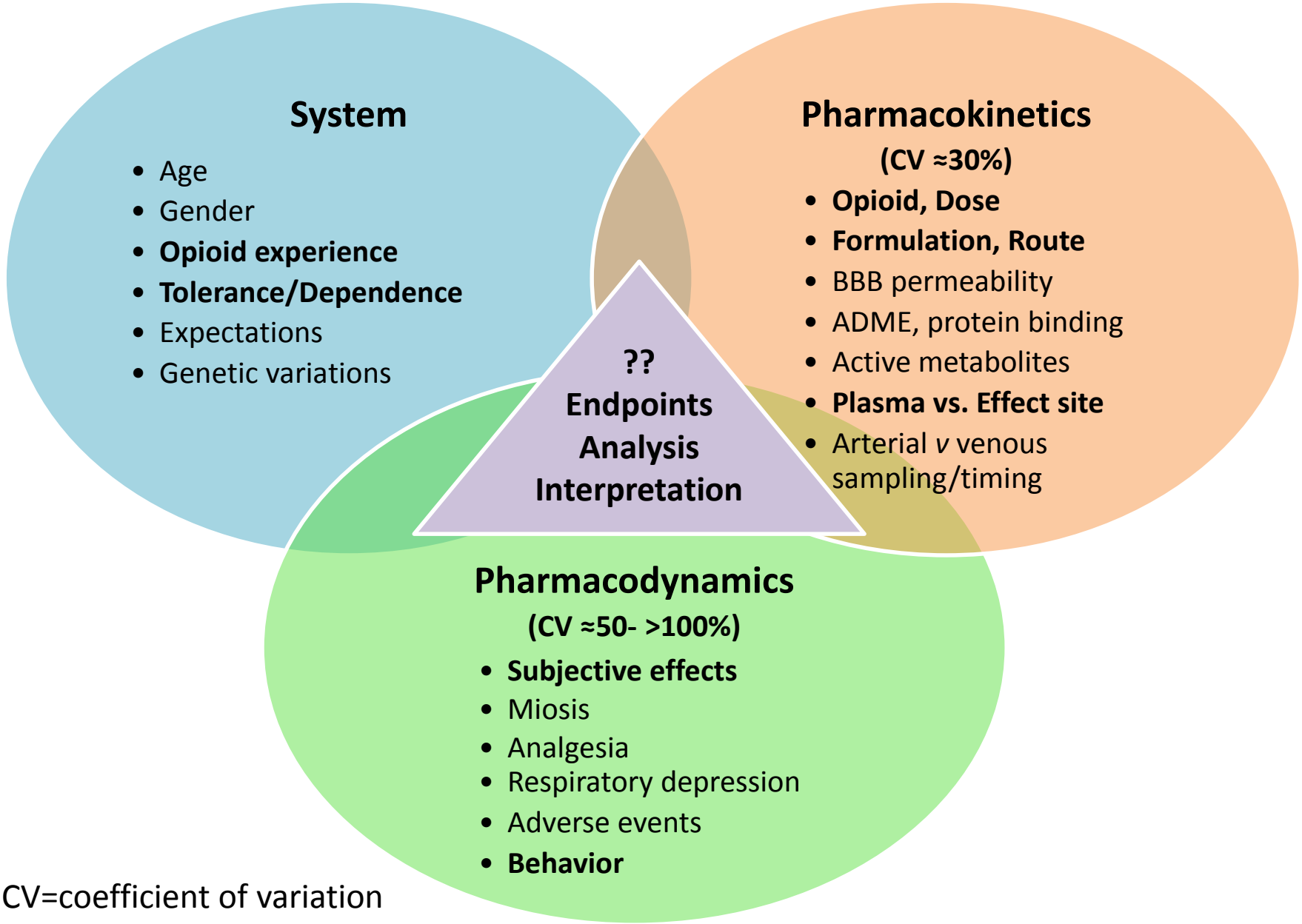
- Goal of PK/PD analysis is to assist in predicting the effect of a drug over time, in relation to exposure
- In terms of abuse, the relationship between rate of rise of [drug] and effect is considered important
  - Fast onset, short duration of action favors repeated self-administration
  - Delaying onset, extending duration of action can reduce immediate reinforcing effect and need to take more drug



Questions

- Can PK assist in predicting subjective response to opioid?
- How can one assess if change in PK profile will be enough to affect PD response?
  - eg, partial defeat of the AD mechanism

PK/PD: Determinants of Variation



CV=coefficient of variation

Assessing the link between opioid exposure and results of a clinical abuse potential study

Recent ADF Examples

When PK/PD relationship might exist

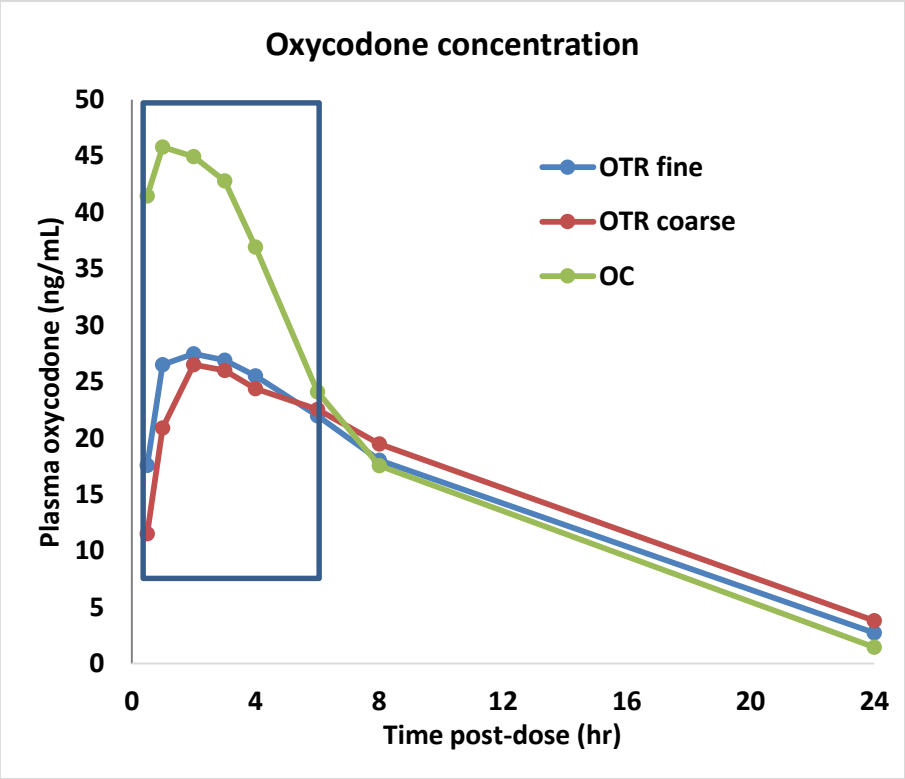
- Physicochemical barrier
  - Resistance to manipulation for oral, IN and IV* administration
- Prodrug
  - Must be cleaved systemically to liberate active moiety
  - Deterrence from IN and IV administration, and possibly oral if limited by saturable process
- Delivery System
  - Modified drug delivery to reduce diversion via multiple routes

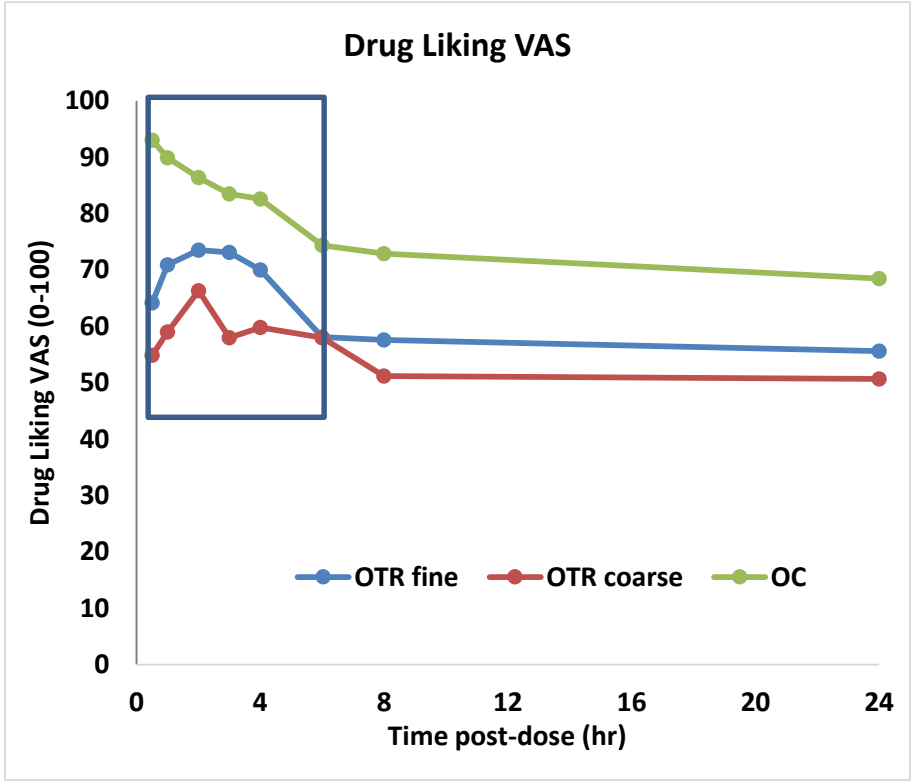
*not generally feasible to administer manipulated product IV

PK/PD of intranasally administered Reformulated OxyContin®

- 5-way crossover study in recreational opioid users with intranasal experience
  - Coarse and fine ground OTR (30 mg)
  - Positive controls: Oxy API and fine ground original OC (30 mg)
  - Placebo control: lactose powder

Time course of effects



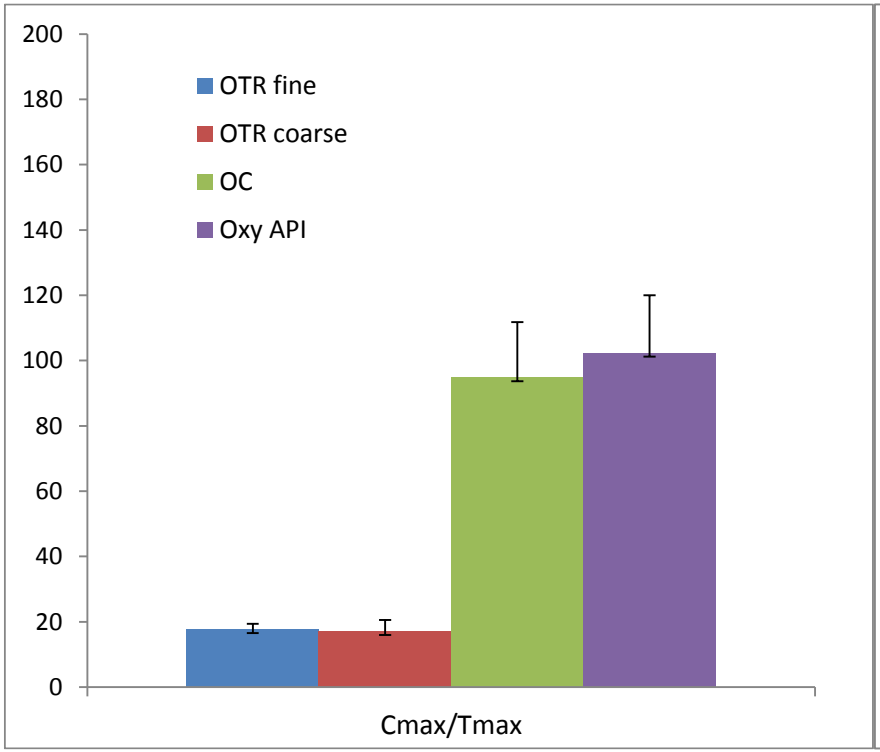


Effects unrelated to drug exposure can impact experience (at the moment and overall)

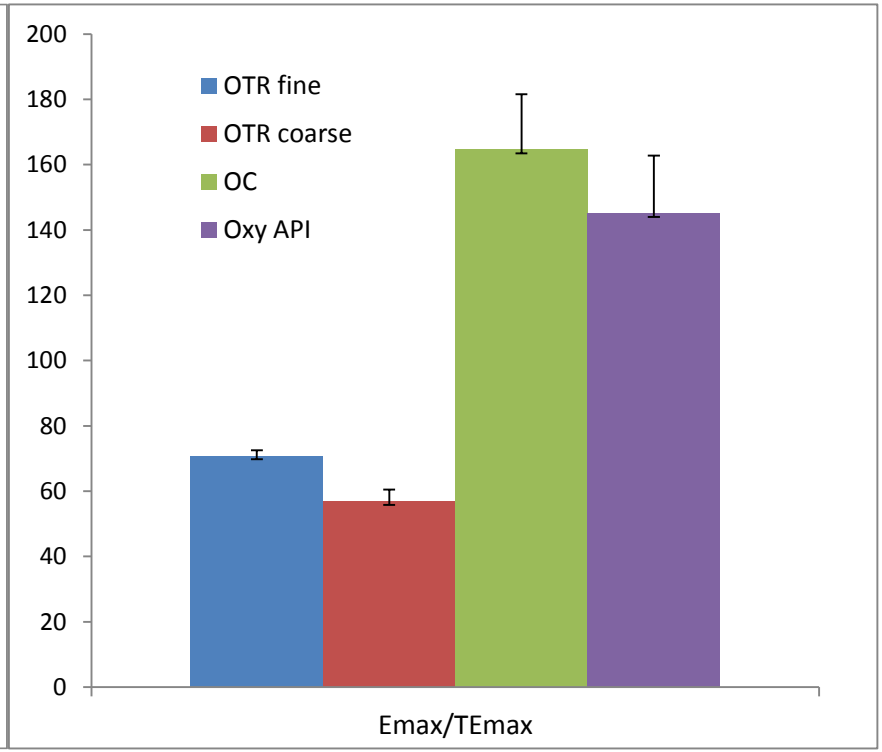
Courtesy of Purdue Pharma; Perrino et al., 2012 CPDD; Harris et al., submitted

Rate of Rise: "Abuse quotient"

- Lower C_{max} and longer T_{max} → lower Abuse Quotient



Oxycodone Pharmacokinetics



Drug Liking Visual Analog Scale

Data courtesy of Purdue Pharma

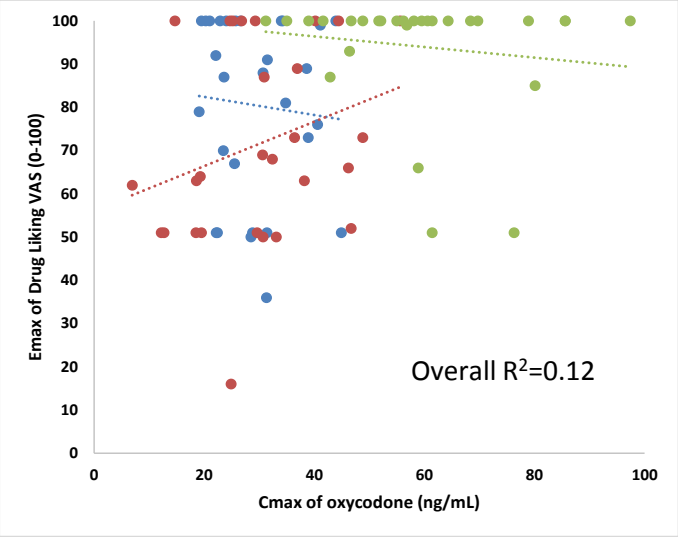
Exposure-Response Relationship

- For reformulated OxyContin®, delaying and lowering C_{max} had significant impact on liking

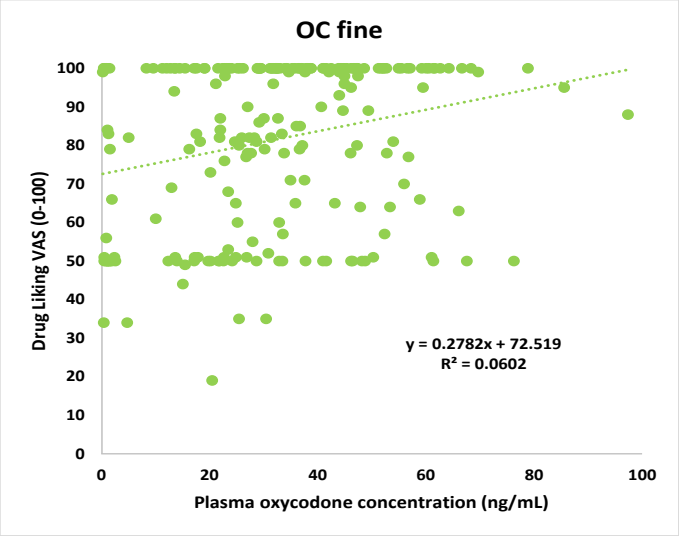
- But if PK “drives” PD, what is concentration-effect relationship?

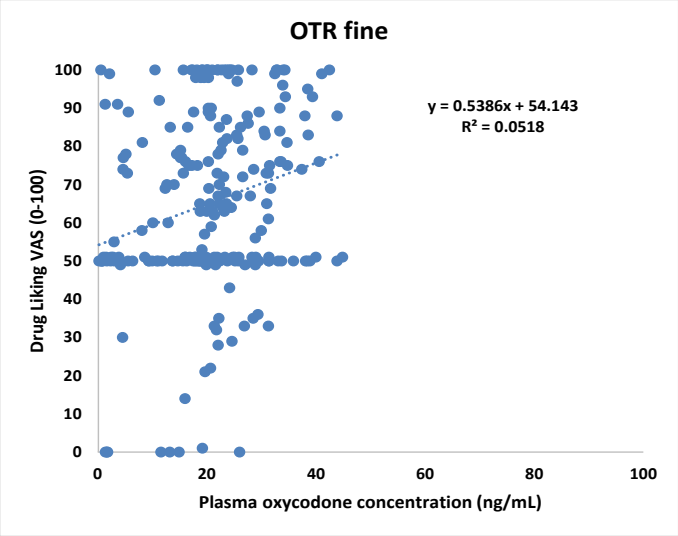
PK/PD Correlations: Subjective Effects

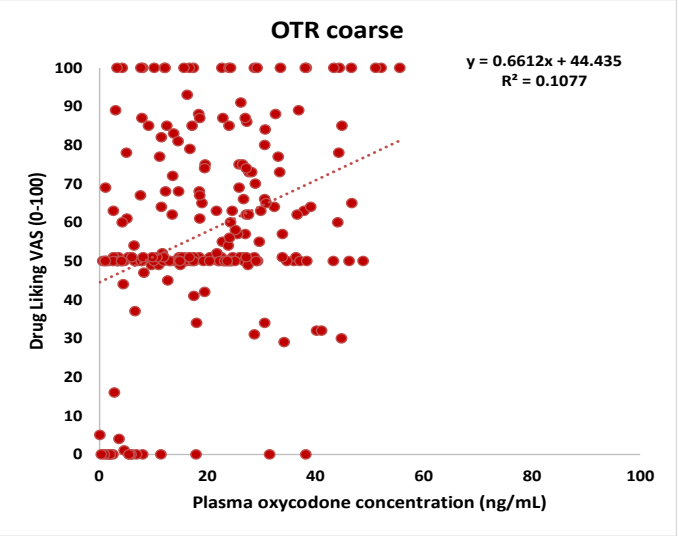
Derived Parameters



By Timepoint



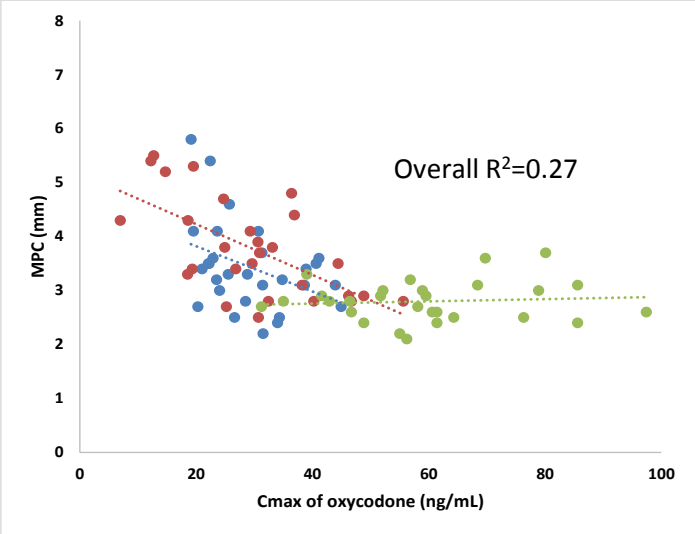




Data courtesy of Purdue Pharma

PK/PD Correlations: Physiological Effects

Derived Parameters



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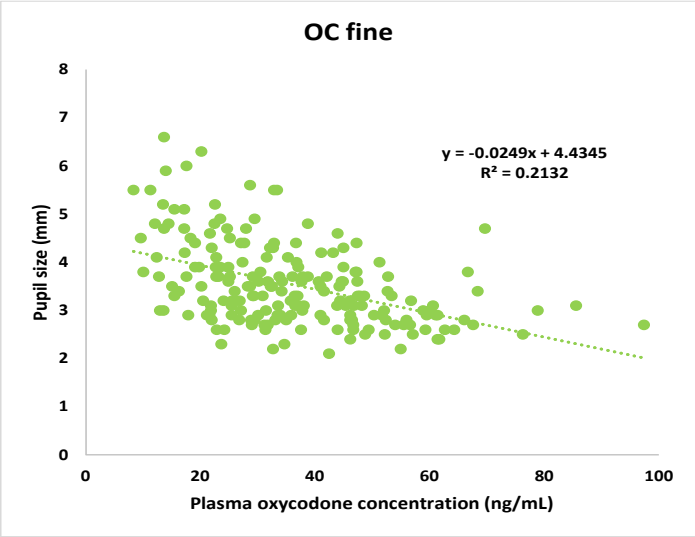
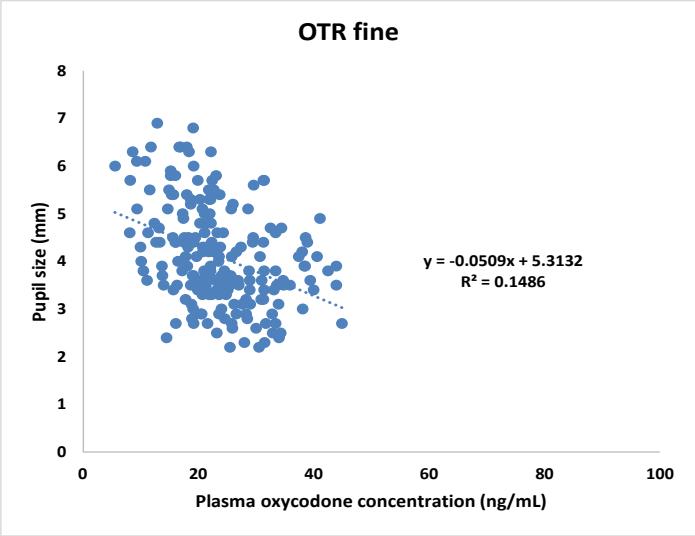
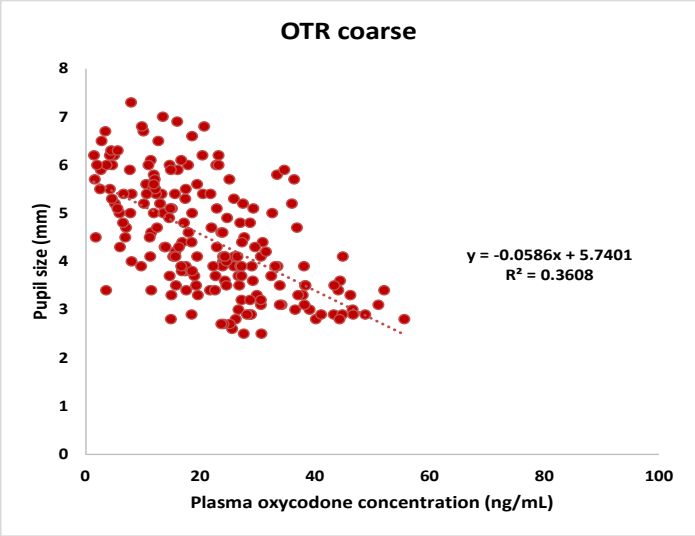






Data courtesy of Purdue Pharma

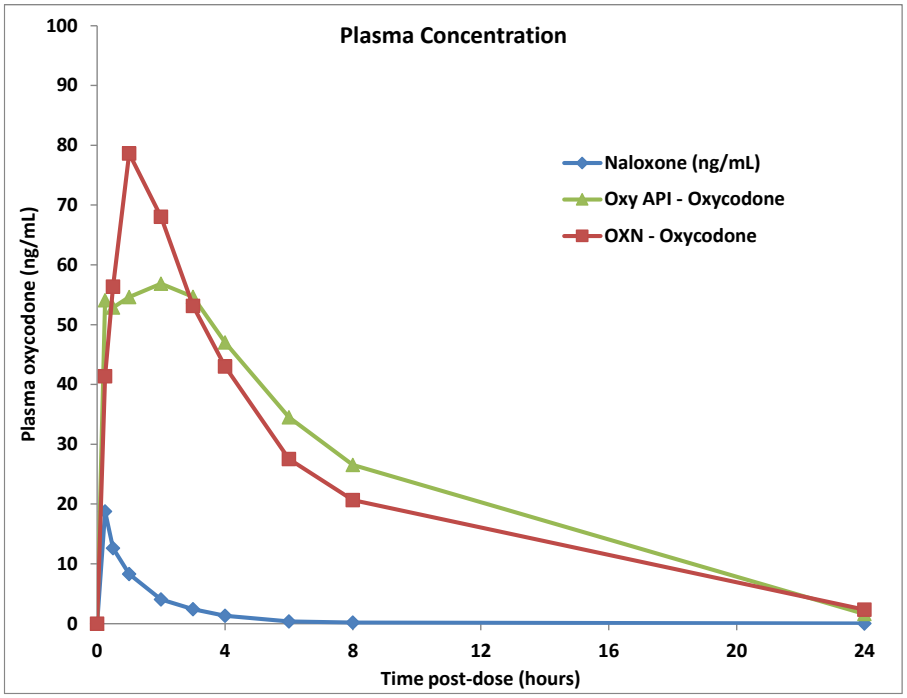
When PK/PD might matter less

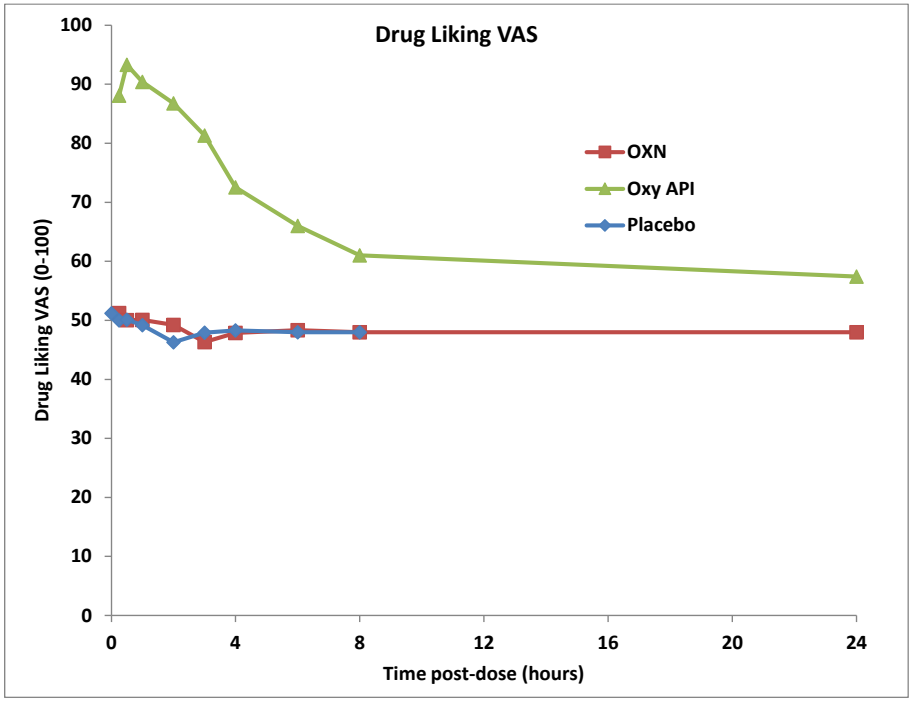
- Opioid agonist-antagonist combinations
  - Antagonist attenuates/reverses effect of opioid
  - Does PK of antagonist help predict response to agonist?
- Aversion
  - Aversive agent not intended to impact exposure to agonist
  - PK would NOT predict overall response to ADF
  - Might still experience *high* from opioid; however, product not *liked*

PK/PD of intranasally administered OXN

- 3-way crossover study in recreational opioid users with intranasal experience
  - Crushed OXN 40/20 mg (oxycodone/naloxone)
  - Positive control: Oxy API 40 mg
  - Placebo control: lactose powder

Time course of effects

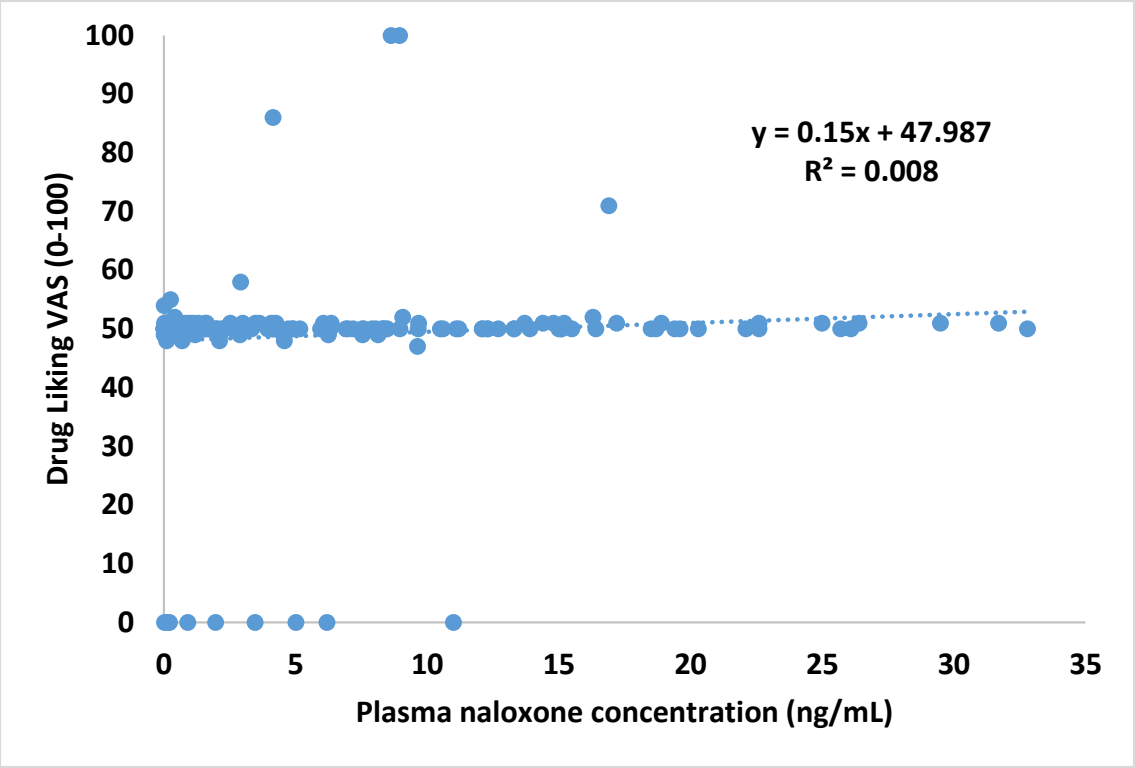




- At 2:1 ratio, OXN significantly reduces Drug Liking to placebo-like levels
- Rate of rise: "Abuse Quotient" (C_{max}/T_{max}) not applicable to opioid agonist-antagonist combinations, such as OXN

Data courtesy of Purdue Pharma

Antagonist PK – Agonist PD



- Highly variable concentrations and lack of concentration-effect relationship of to-be-marketed formulation
- Relationship between antagonist PK and agonist PD typically evaluated earlier in development in dose-ranging trials – ie, dose-effect

Data courtesy of Purdue Pharma

Conclusions

- Relationship between PK and PD of abuse potential is weak and highly variable
- Effects unrelated to opioid exposure impact subject's experience
- Clinical PD study necessary to determine potential for abuse (or its deterrence)
- PK alone cannot be used as substitute in abuse potential assessment