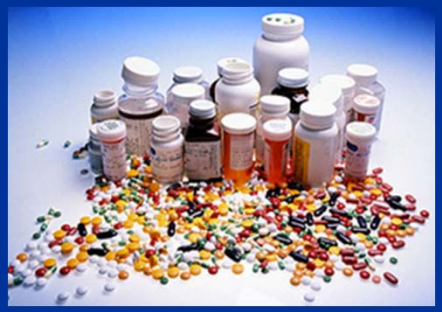
The Role and Interpretation of Pharmacokinetic Parameters in Assessment of Abuse Liability: Category 2 Studies



Sharon L. Walsh, Ph.D.
Center on Drug and Alcohol Research
Department of Behavioral Science
University of Kentucky

Abuse Deterrence Formulation Science Meeting
September 30 – October 1

Outline

- Describe the role for pharmacokinetic studies as defined in the FDA Draft Guidance on abuse deterrent formulations
- Discuss specific pharmacokinetic parameters and their potential role
- Distinguish between those questions that can be answered by pharmacokinetics alone AND those that cannot

I. Stated Objectives for Pharmacokinetic Studies in the Draft Guidance

- To understand the *in vivo* properties of the abuse deterrent formulation by comparing the PK profile of the manipulated formulation with
  - the intact formulation
  - the intact and manipulated formulations of a comparator drug(s)
  - by one (or more) routes of administration

II. Revelant Pharmacokinetic Parameters Specified by the Draft Guidance*

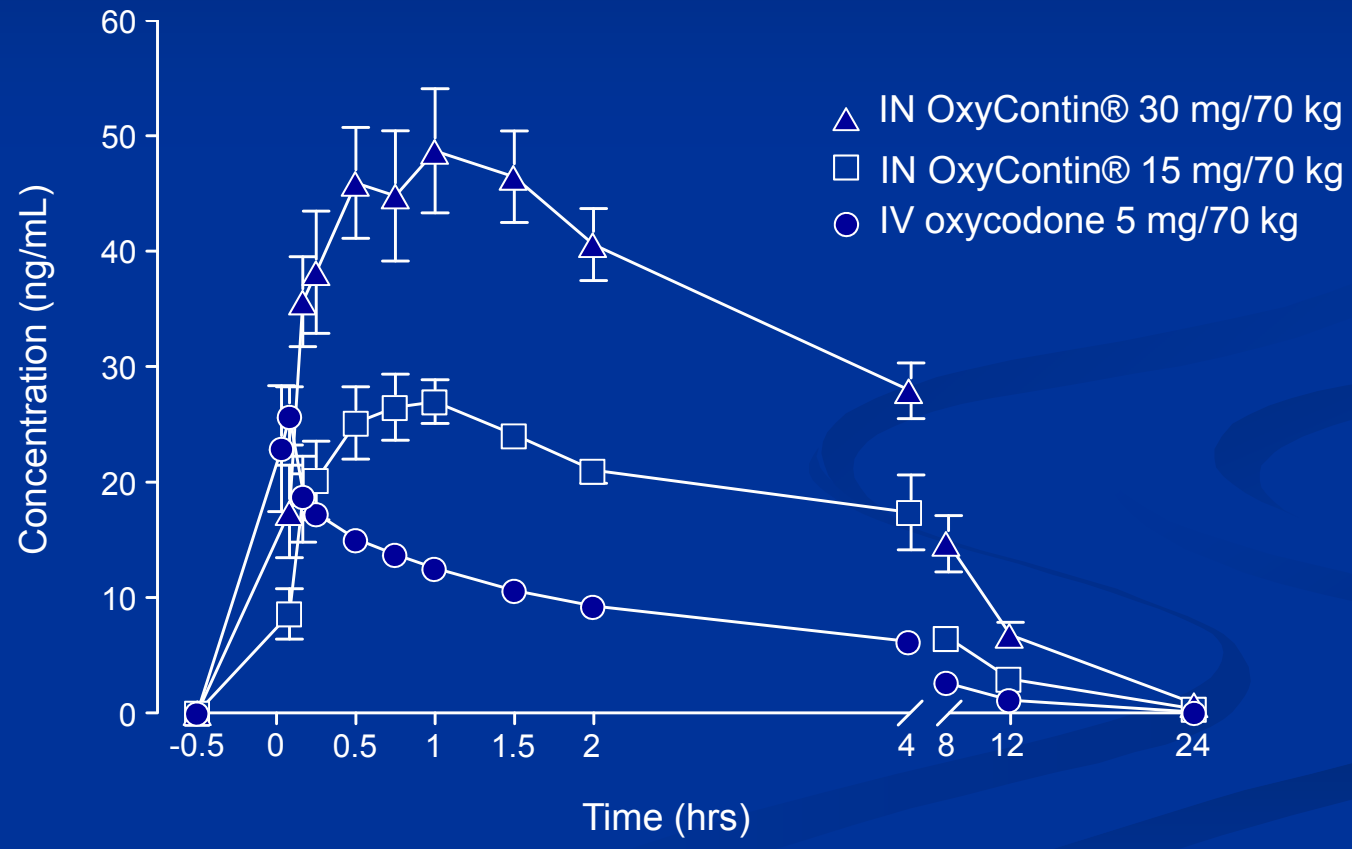
C_{max}	maximum concentration
T_{max}	time to maximum concentration
AUC	area-under-the-curve; AUC_{0-t} $AUC_{0-\infty}$ and/ or relevant truncated time [i.e., AUC_{0-30}]
T ½	terminal elimination half-life

*Parent drug and any relevant active metabolites

What Can Be Learned From These Specified Parameters?

- It is generally accepted that abuse liability of a CNS drug can be increased by
  - Increasing the C_{max} (peak concentration)
  - Decreasing the T_{max} (the time to reach C_{max})
  - Or doing both
- Human studies have demonstrated that these changes may result in greater scores on pharmacodynamic outcomes related to abuse potential (i.e., euphoria, liking, etc.)

Oxycodone Concentrations



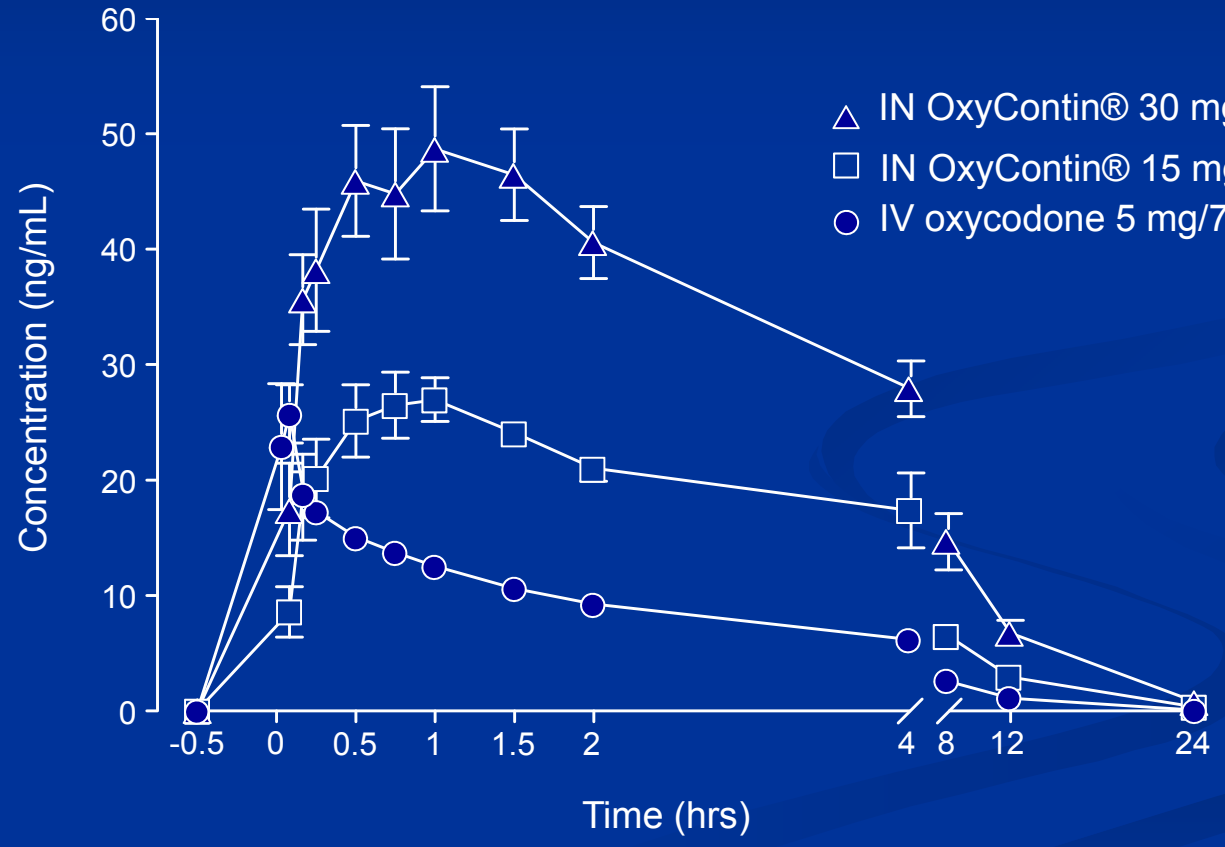
Lofwall, Moody, Fang and Walsh (2011) J Clin Pharmacol, 52: 600-606.

Intranasal

Plasma t_{max} ~60 min

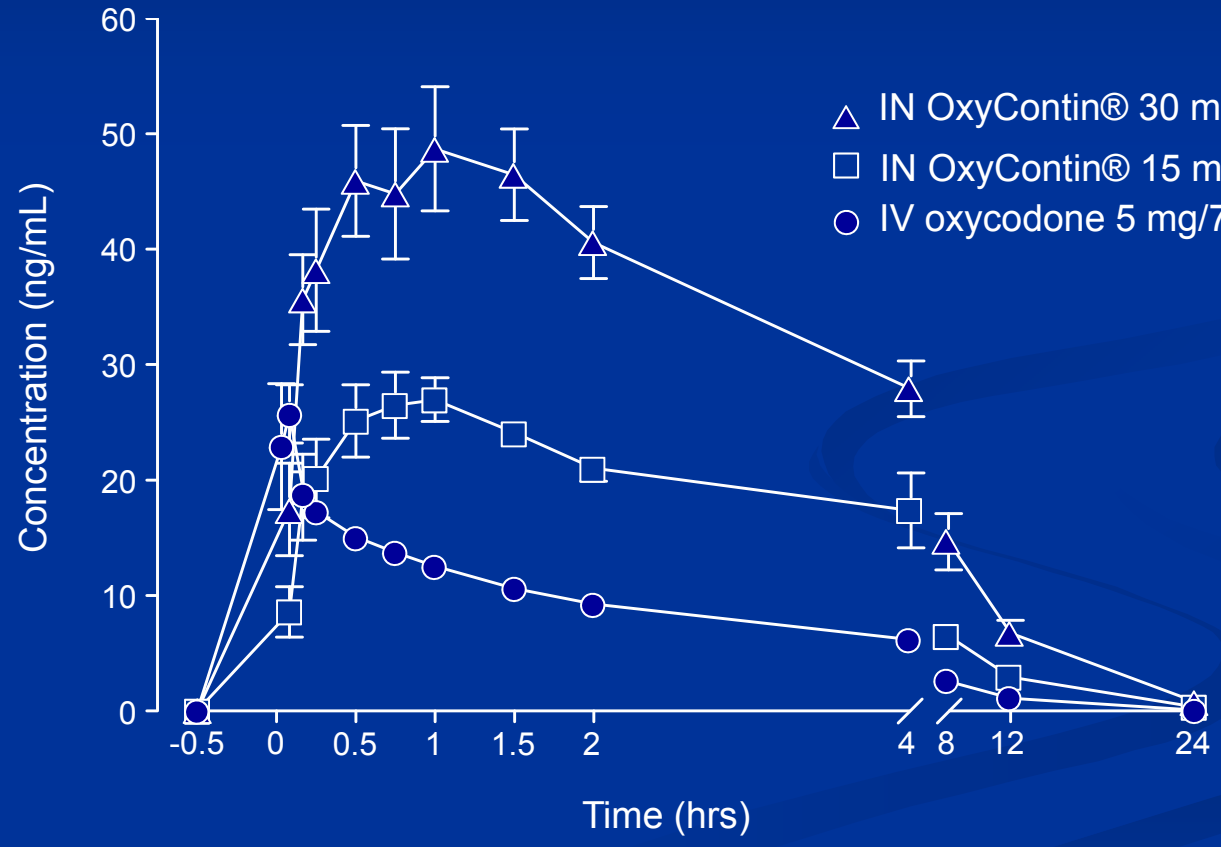
Oral

Plasma t_{max} ~60-90 min



Lofwall, Moody, Fang and Walsh (2011), J Clin Pharmacol, 52: 600-606.

Intranasal		Oral	
Plasma t_{max}	~60 min	Plasma t_{max}	~60-90 min
Bioavailability	~76%	Bioavailability	~60%

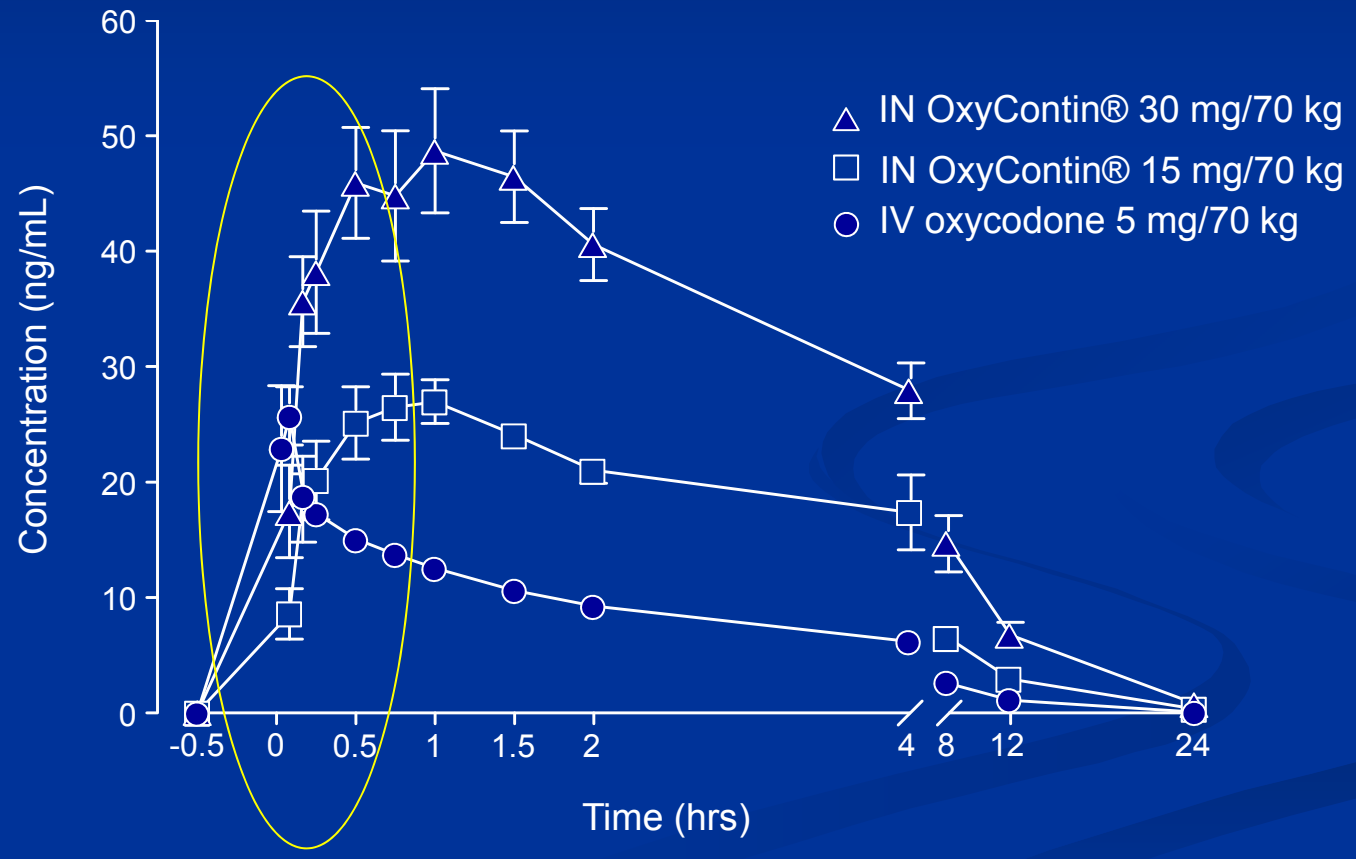


Lofwall, Moody, Fang and Walsh (2011), J Clin Pharmacol, 52: 600-606.

III. Guidance Recommends Examination of the Rate of Rise of Drug Concentration

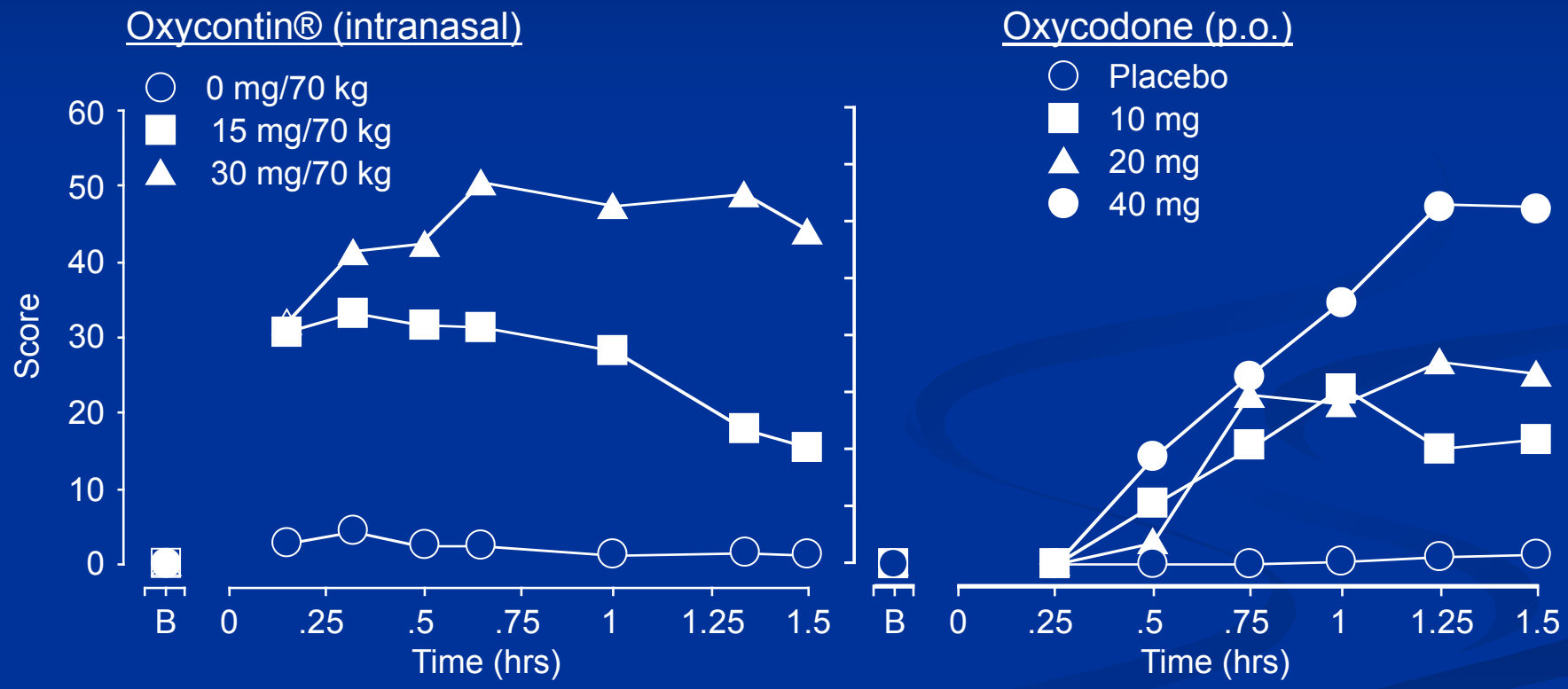
- Based on the observation that drug delivered/absorbed more rapidly can lead to increased abuse potential
- Examination of the rate of rise requires an appropriate specimen collection schedule designed to capture onset, peak and offset of effects for formulation and comparators (intact and manipulated)

Oxycodone Concentrations



Lofwall, Moody, Fang and Walsh (2011), J Clin Pharmacol, 52: 600-606.

“How Much Do You Like the Drug?”



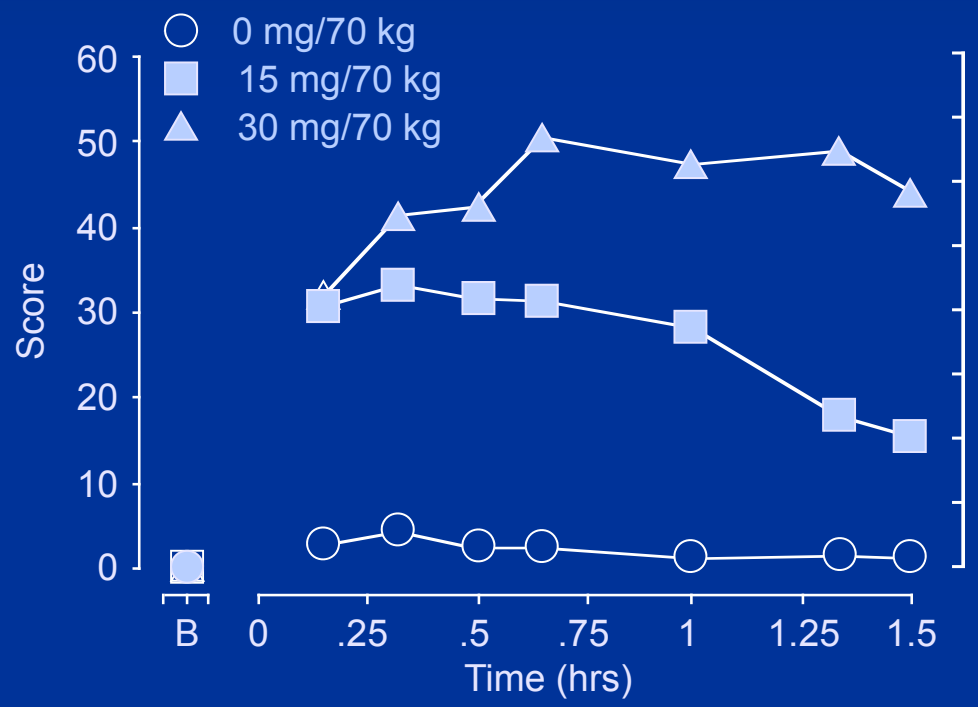
Lofwall, Nuzzo & Walsh (2012) Drug and Alcohol Dependence, 123: 229-238.

Walsh, Nuzzo, Lofwall & Holtman (2008) Drug and Alcohol Dependence, 98: 191-202.

"How Much Do You Like the Drug?"

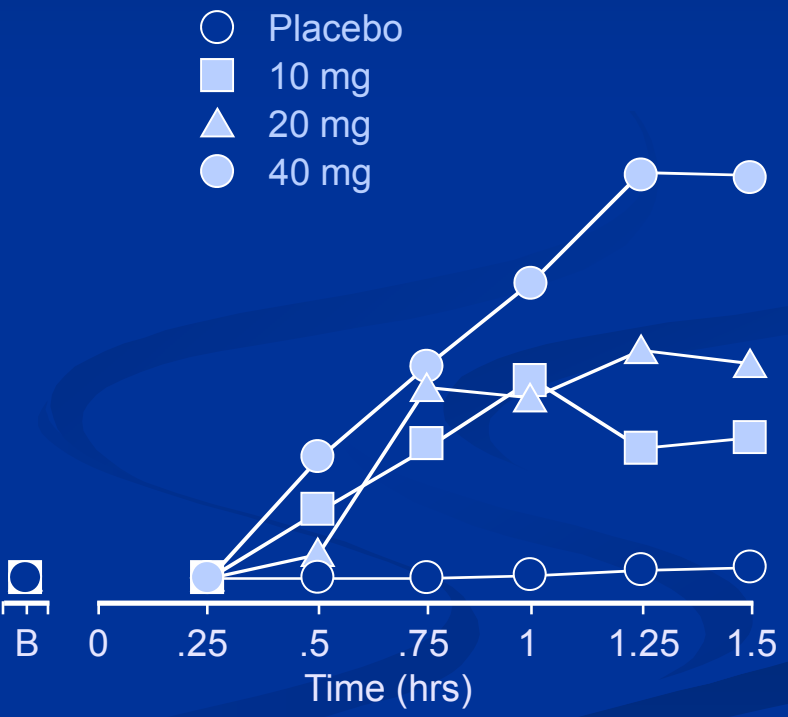
t_{max} 40 min

Oxycontin® (intranasal)

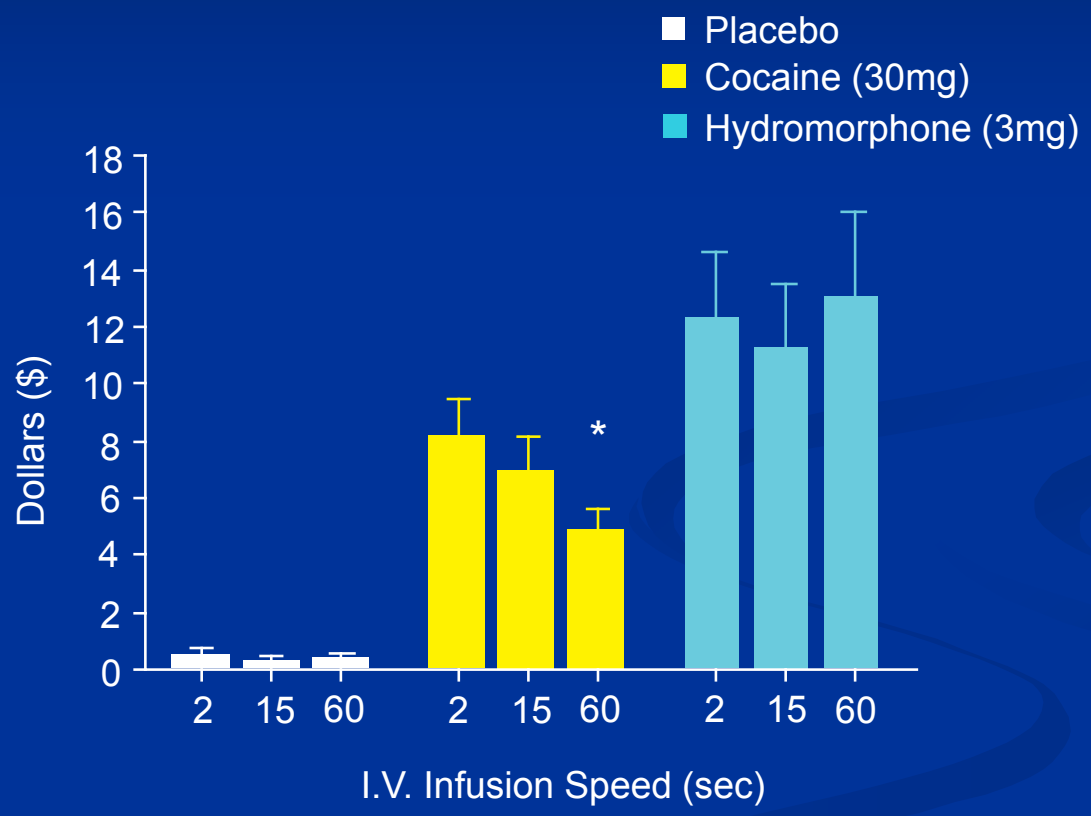


t_{max} 73 min

Oxycodone (p.o.)



Estimated Street Value ($)



Abreu, Bigelow, Fleisher & Walsh (2001) Psychopharmacology: 154: 76-84

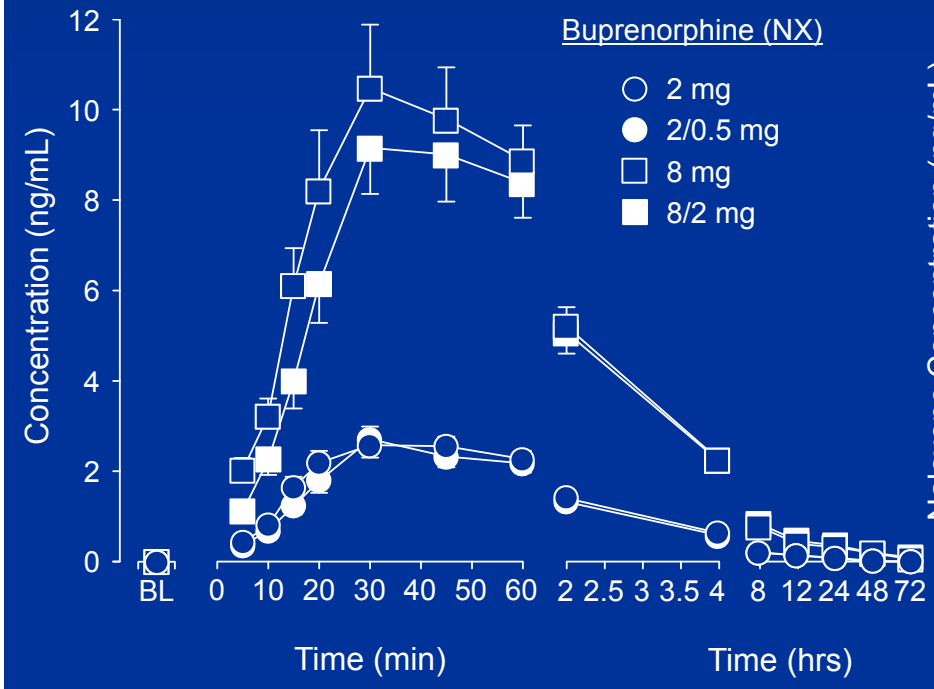
Assessment of ADFs Using Physical/Chemical Barriers

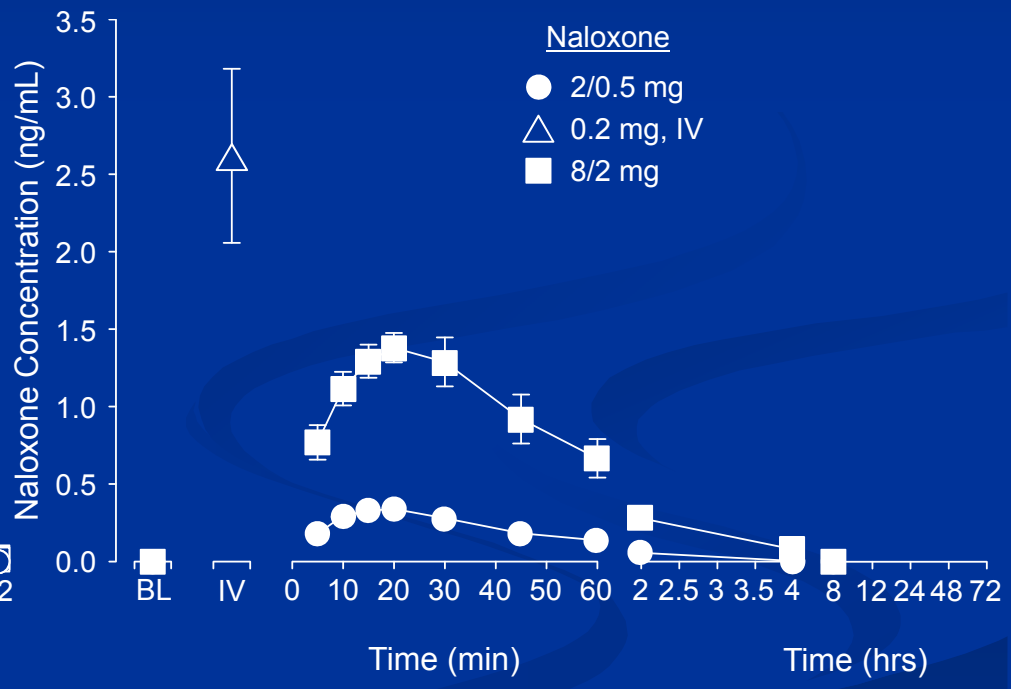
- All of the pharmacokinetic parameters (i.e., T_{max}, C_{max}, AUC, bioavailability) can inform the relative resistance to manipulation by examining of drug exposure after dosing when the drug is
  - Swallowed whole
  - Crushed and swallowed
  - Crushed and snorted
  - Crushed and smoked
  - Crushed, dissolved and injected

Inclusion of Agonist/Antagonist Combinations or Aversive Agents

- Pharmacokinetic data can demonstrate absorption/distribution of the therapeutic AND of the aversive agent(s) under differential tampering conditions
- However, the pharmacokinetic data alone cannot address the abuse liability because the subjective experience of the presence or absence of the aversive agent must be captured through pharmacodynamic outcomes

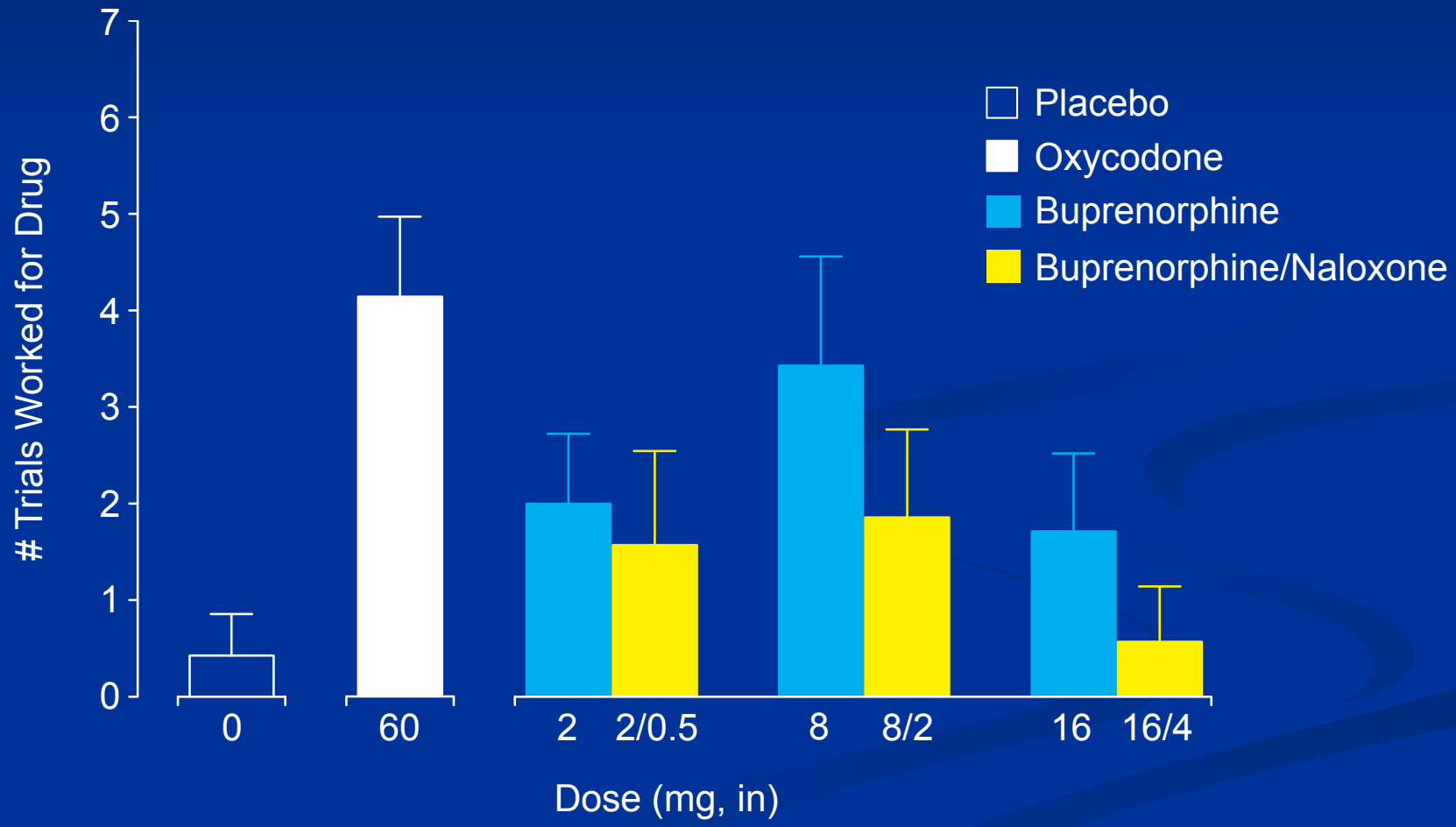
Misuse of Buprenorphine/Naloxone by the Intranasal Route





Middleton, Nuzzo, Lofwall, Moody & Walsh (2010) Addiction, 106: 1460-1473.

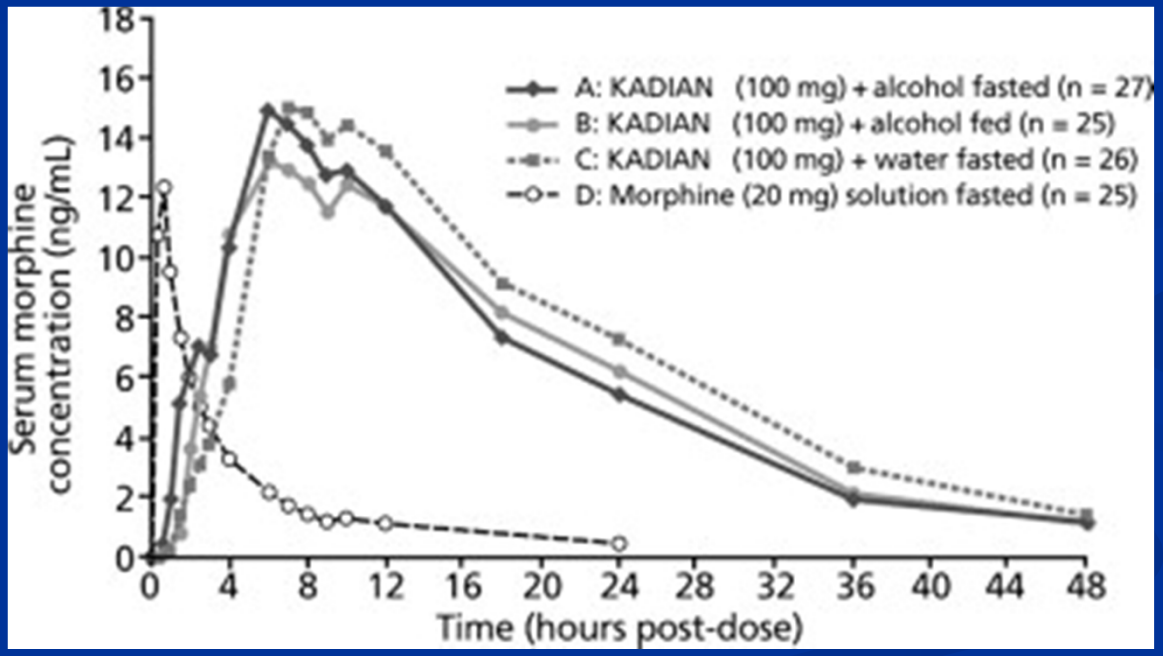
Self-Administration in Opioid Dependent Subjects (30 mg oxycodone, QID p.o.)



Walsh, Nuzzo and Lofwall, unpublished data

IV. Additional FDA Guidance Recommendations

- Data should also be provided if food and alcohol alter the pharmacokinetics of the formulation



Johnson, Wagner, Sun and Stauffer (2008) Journal of Pain, 9: 330-336.

V. Final Considerations from the Guidance

- Study design should be informed by the Category 1 studies (in vitro manipulation and extraction)
- Studies are an opportunity to collect AE reports, including those specific to the manipulations related to misuse (e.g., tolerability/discomfort with snorting or injecting)
- Differences may arise from the formulation itself, properties after tampering, and/or excipients

Summary

- To answer questions directly related to abuse liability (and protection against it), parameters such as C_{max}, T_{max} and AUC will nearly always need to be evaluated in the context of pharmacodynamic outcomes
- Pharmacokinetic data alone can generally answer questions about
  - Bioequivalence
  - Bioavailability
  - Food Effects
  - Dose Dumping (e.g., alcohol)

Conclusions

- While the FDA requires pharmacokinetic studies to evaluate an abuse deterrent formulation when intact and tampered in comparison to a specified control agent, in most cases, the pharmacokinetic findings alone cannot fully inform the question of abuse potential in the absence of pharmacodynamic data

Conflict of Interest

- Served as consultant to DemRX and Eli Lilly & Co.
- Received compensation for teaching physicians on good practices for treatment of opioid dependence (PCM Scientific through an unrestricted grant from Reckitt Benckiser)

Sample Questionnaire

When I snorted this drug, my nose or throat felt:

Burning	0	1	2	3	4
Tingling	0	1	2	3	4
Itching	0	1	2	3	4
Pain	0	1	2	3	4
Congestion	0	1	2	3	4
Numbness	0	1	2	3	4
Stinging	0	1	2	3	4
Thirsty	0	1	2	3	4
Dry Mouth	0	1	2	3	4

Was it difficult to snort the amount of powder provided?

_____ NO _____ YES

Sample Questionnaire

When I snorted this drug, my nose or throat felt:

Burning	0	1	2	3	4
Tingling	0	1	2	3	4
Itching	0	1	2	3	4
Pain	0	1	2	3	4
Congestion	0	1	2	3	4
Numbness	0	1	2	3	4
Stinging	0	1	2	3	4
Thirsty	0	1	2	3	4
Dry Mouth	0	1	2	3	4

Was it difficult to snort the amount of powder provided?

NO _____ YES _____