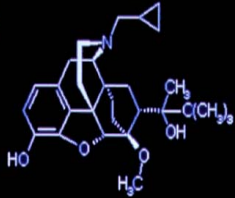
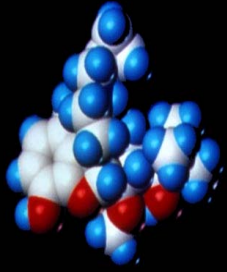


BUPRENORPHINE



Buprenorphine's Effects on Brain Function and Behavior: Clinical Implications

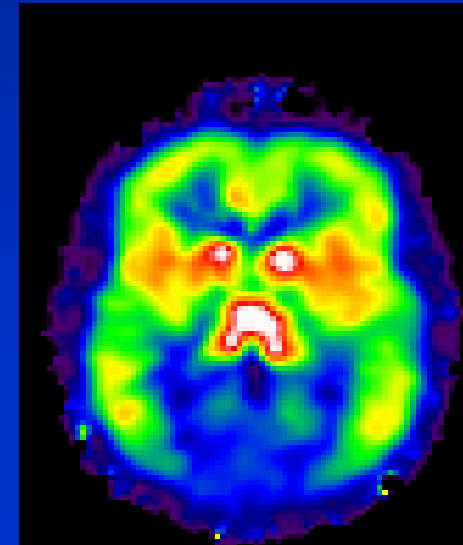
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Acknowledgements

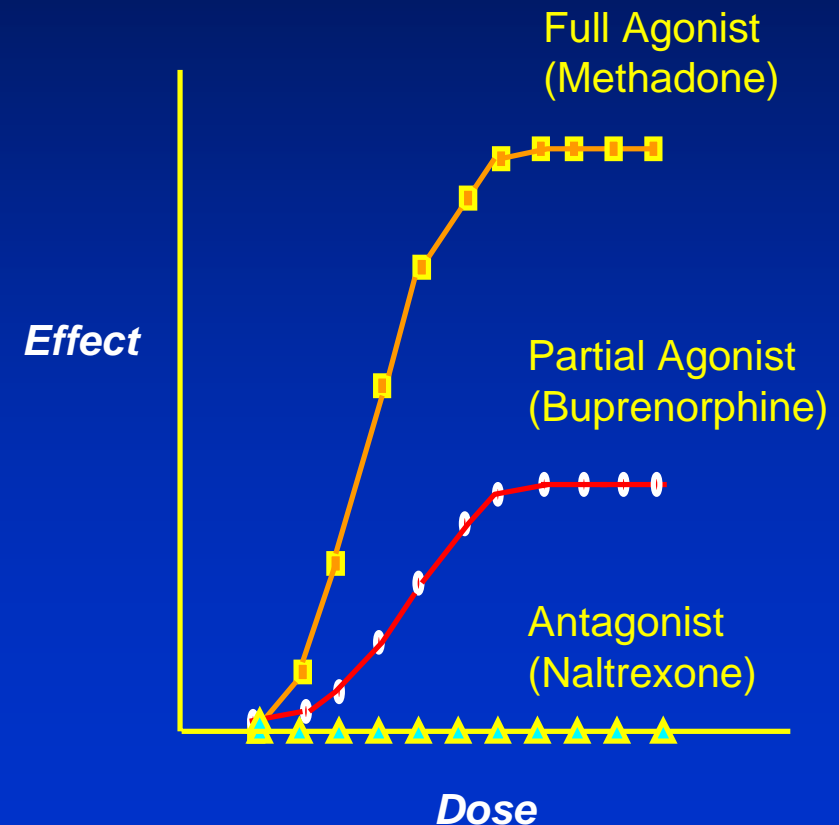
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***The pharmacology of buprenorphine:
How does it work?***

The Pharmacology of Buprenorphine

Opioid Agonists: Pharmacological Actions at μ ORs

- Agonists
 - Target biological actions that perpetuate heroin use (mediated by μ ORs)
 - Prevent opioid withdrawal and craving
 - Decrease euphoric/reinforcing effects of heroin
- Full agonists (e.g., methadone, heroin)
 - Occupy and activate the opioid receptor
 - Increasing drug doses produce greater effects until maximum effect is achieved
- Partial agonists (e.g., buprenorphine)
 - Occupy and activate the receptor (like a full agonist)
 - Produce less of a maximum effect



The Pharmacology of Buprenorphine

- Partial agonist at *mu* receptor
 - less risk of respiratory depression
 - lower level of physical dependence
 - lower abuse liability
- High affinity for *mu* receptor
 - competes with other opioids and blocks their effects
 - slow dissociation leads to prolonged therapeutic effect

***Buprenorphine's effects on brain
opioid receptors and behavior of
heroin abusers***

Brain/Behavior Research Program

- Rationale

- Clinical efficacy of opioid maintenance is believed to result from a medication's ability to decrease μ OR availability, thereby replacing agonist effects, alleviating withdrawal symptoms and blocking heroin's effects.

- Aim

- Examine the clinical consequences of variations in *mu*-receptor binding in heroin dependent individuals

- Strategies

- Study 1: Different maintenance doses of BUP
- Study 2: Different times since last (fixed) maintenance dose

Brain and Behavioral Measures

- *Mu*-opioid receptor availability
- Pharmacokinetics
 - 24 hr profile ($t = 0, 1, 2, 3, 4, 8$ and 24 hr after daily dose)
 - Single blood draw prior to each PET scan
- Baseline opioid symptoms
 - Agonist and withdrawal scales
- Response to Hydromorphone (Dilaudid™)
 - 24 mg IM injection

Brain Imaging and Analysis 1

- Measure *in vivo* μ OR availability using radiotracer [^{11}C]-carfentanil
 - High selectivity and affinity
 - Given at low doses that don't produce a drug effect
 - Think of tracer like heroin (binds to the same receptors)
- Use Positron Emission Tomography (PET) imaging to assess the extent to which BUP binds to μ ORs, as revealed by displacement of [^{11}C]-carfentanil
- So, BUP binding to μ ORs is the complement of μ OR availability

Brain Imaging and Analysis 2

- Receptor binding images (PET) were co-registered with anatomical brain map (MRI)
- Regions of interest
 - Inferior frontal cortex, anterior cingulate, nucleus accumbens, caudate, thalamus, amygdala
 - Global measure

Participant Screening

- Heroin dependent volunteers
 - Males and females, ages 18-50
 - Not seeking drug abuse treatment
 - Willing to take BUP daily and live on inpatient unit for 2 weeks
- Comprehensive medical and psychiatric screening
 - Physically healthy
 - No current DSM-IV disorders (except nicotine dependence)
 - Adequate IV access

Participant Characteristics

- 40 years old (range, 30-50)
- Males > females
- African-American > Caucasian
- 15 years heroin use (range, 5-30)
- \$300/week spent on heroin (range, \$150-\$700)
- Occasional other drug use (cocaine, benzos, cannabis)

Study 1: Vary Buprenorphine Maintenance Dose

(Greenwald et al. 2003; Neuropsychopharmacology)

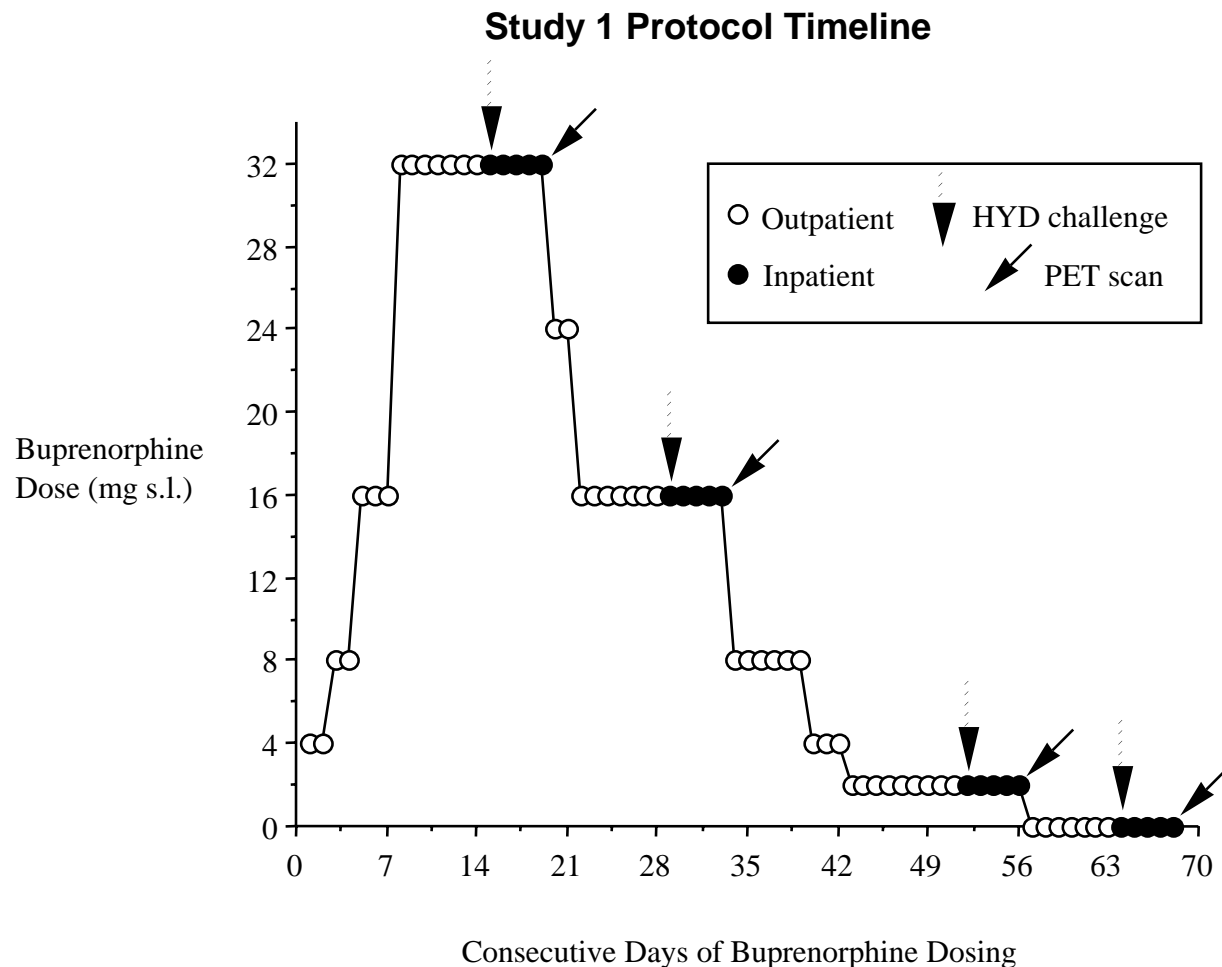
- Determine whether a wide range of BUP doses (32, 16 and 2 mg/day) alters μ OR availability relative to placebo (0 mg/day)
- Each volunteer was tested in all 4 conditions, thereby serving as his/her own control
- Question: Do BUP dose-related variations in μ OR availability correlate with BUP plasma levels, opioid withdrawal symptoms, and the ability of BUP to block effects of hydromorphone?

– On different study weeks, heroin-dependent volunteers received BUP 32 mg/day, 16 mg/day, 2 mg/day then 0 mg/day (detoxification). Procedures were conducted inpatient to minimize illicit drug use.

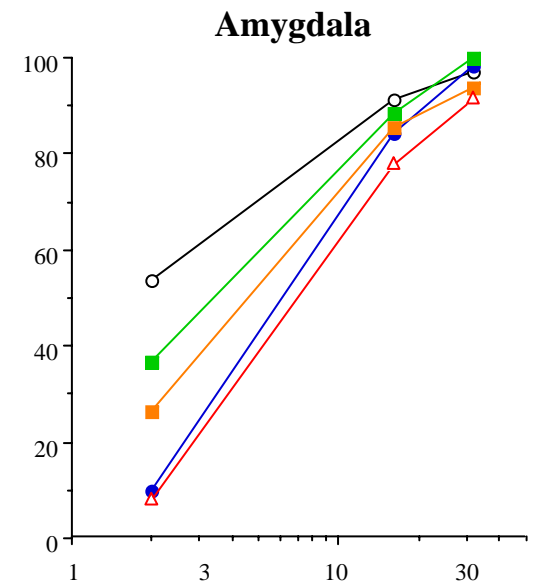
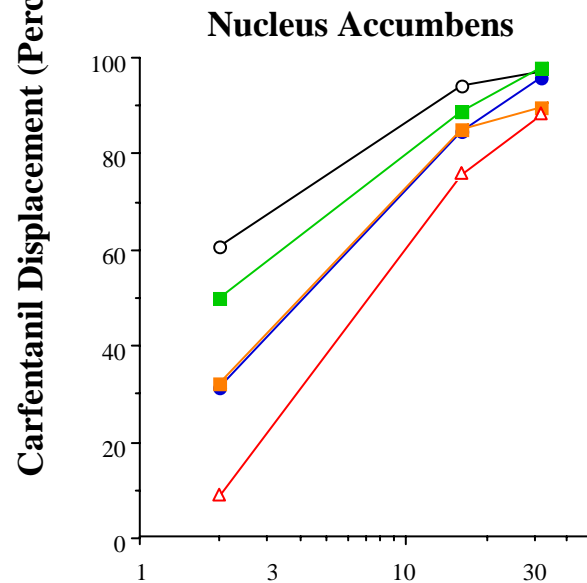
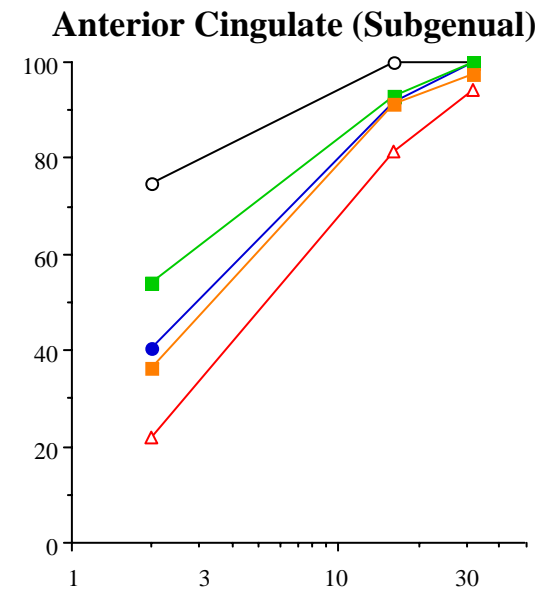
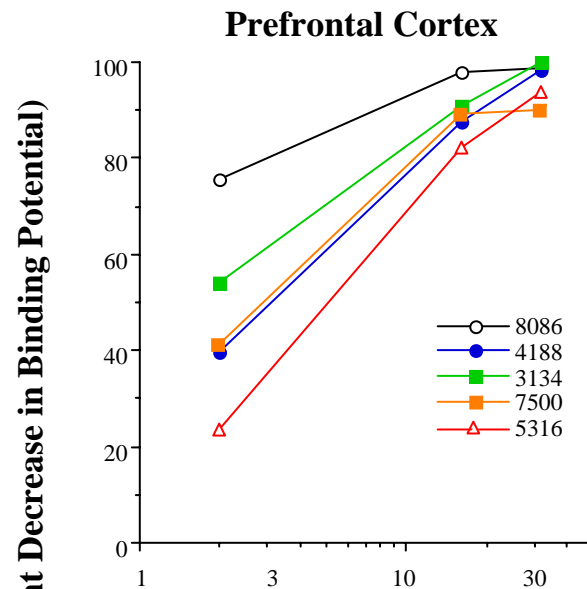
– At each BUP maintenance dose, used PET and [C¹¹]-carfentanil to measure μ OR binding at 4 hr after the daily dose.

– Blood samples were collected over 24 hrs to measure plasma levels

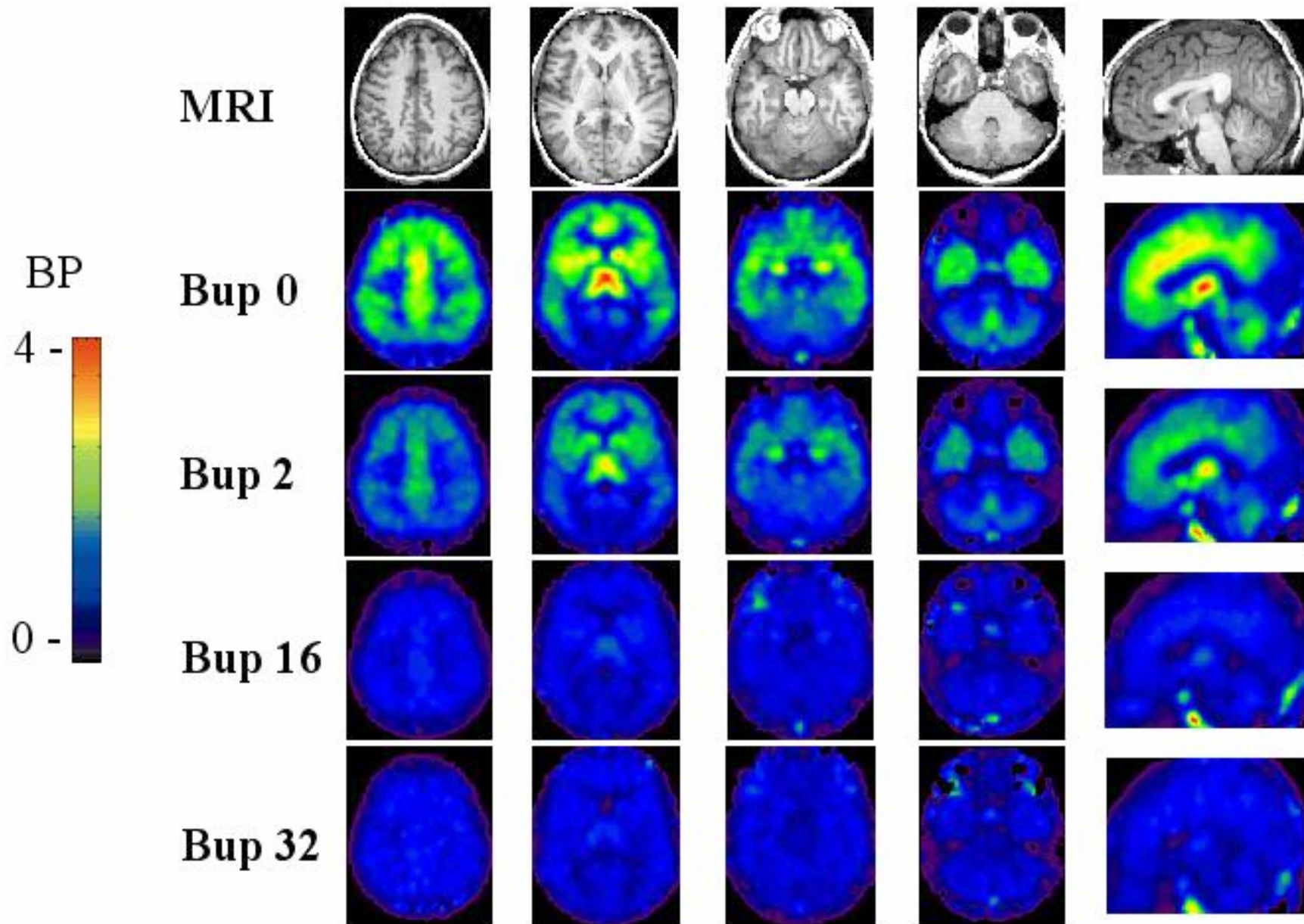
– Subjects also received challenge doses of hydromorphone (HYD), a heroin-like μ OR agonist, to test BUP's blockade ability at each dose (i.e. level of μ OR occupancy).



- Changes from 0 mg (placebo) in several brain regions for the five volunteers.
- Dose-response for all participants.
- No additional binding effect of 32 mg/day, suggesting that 16 mg/day is sufficient to occupy human brain μ ORs.
- Greatest inter-subject variability at the low (2 mg/day) dose.

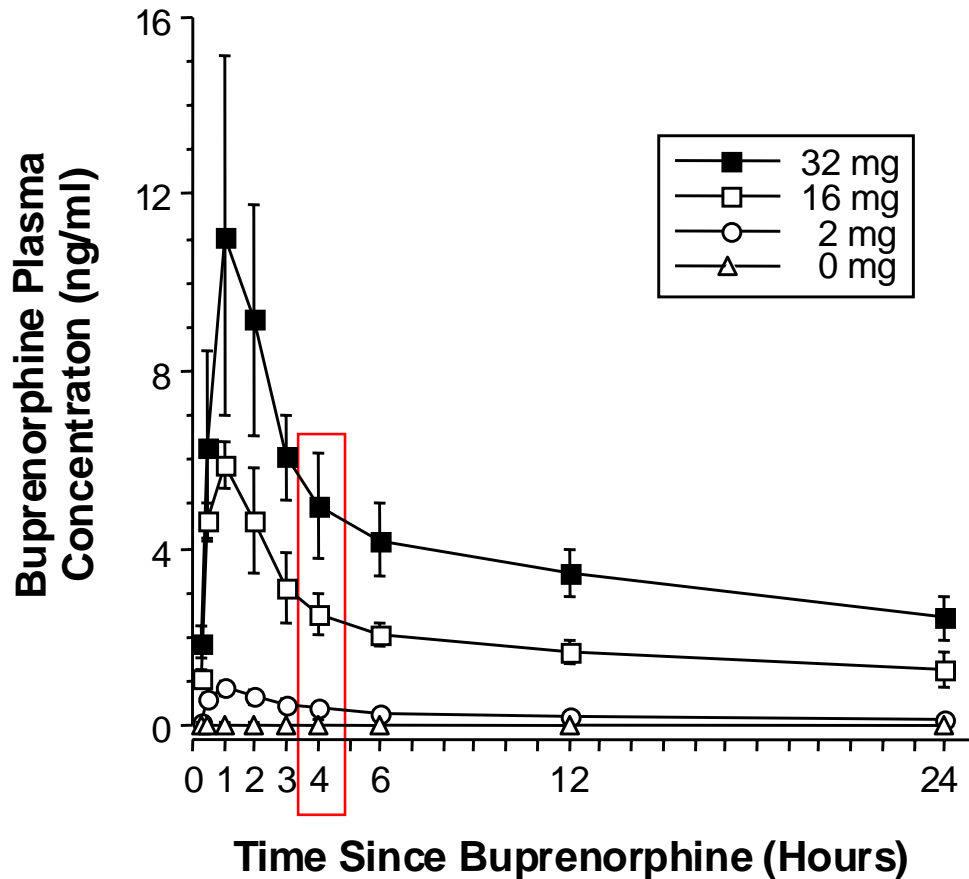


Buprenorphine Tablet Dose

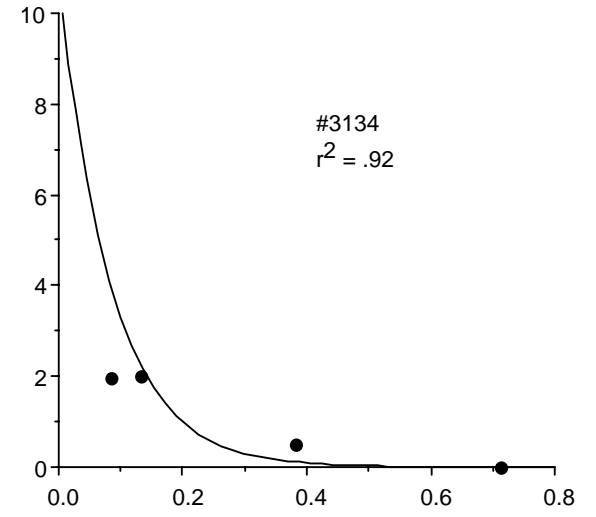
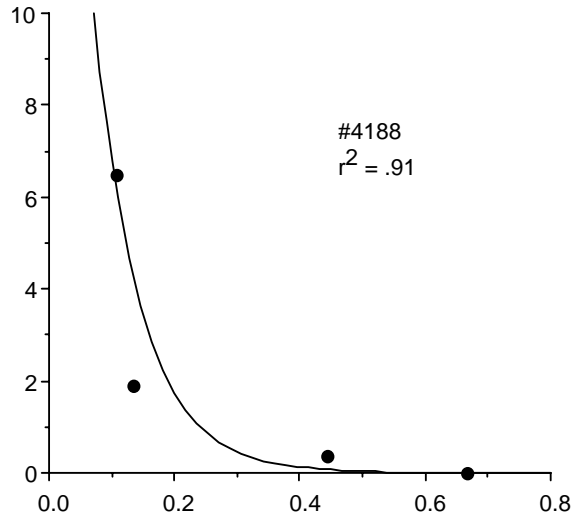
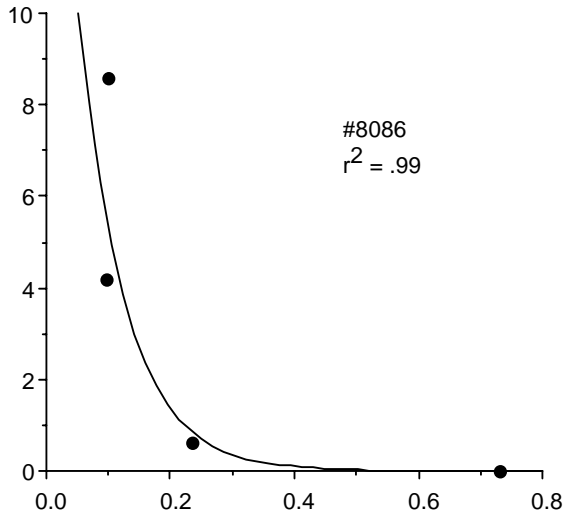


Buprenorphine 24 hr Pharmacokinetics

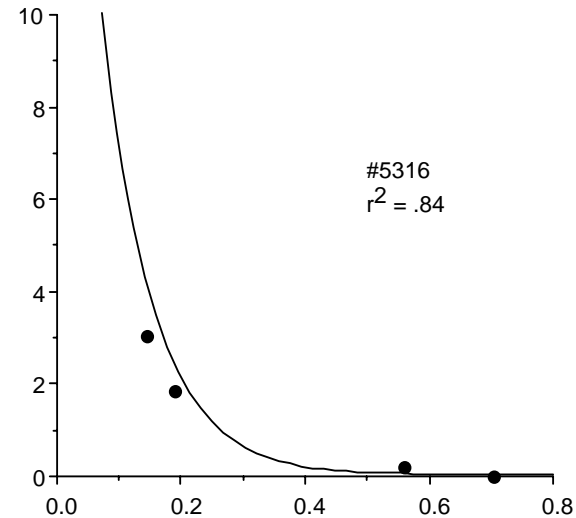
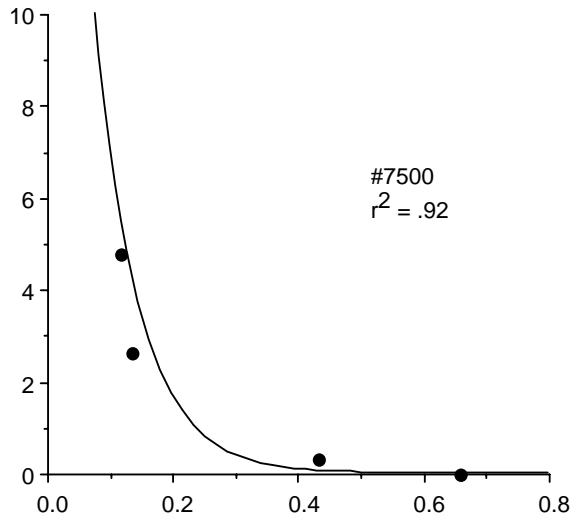
BUP Dose	Tmax (hr)	Cmax (ng/ml)	AUC
2 mg	0.9 + 0.1	0.3 + 0.1	6.5 + 1.6
16 mg	1.2 + 0.2	6.3 + 0.9	48.6 + 8.0
32 mg	1.2 + 0.2	13.2 + 4.2	96.0 + 16.1



μ OR Availability vs. Plasma Level 4 hr After Dose

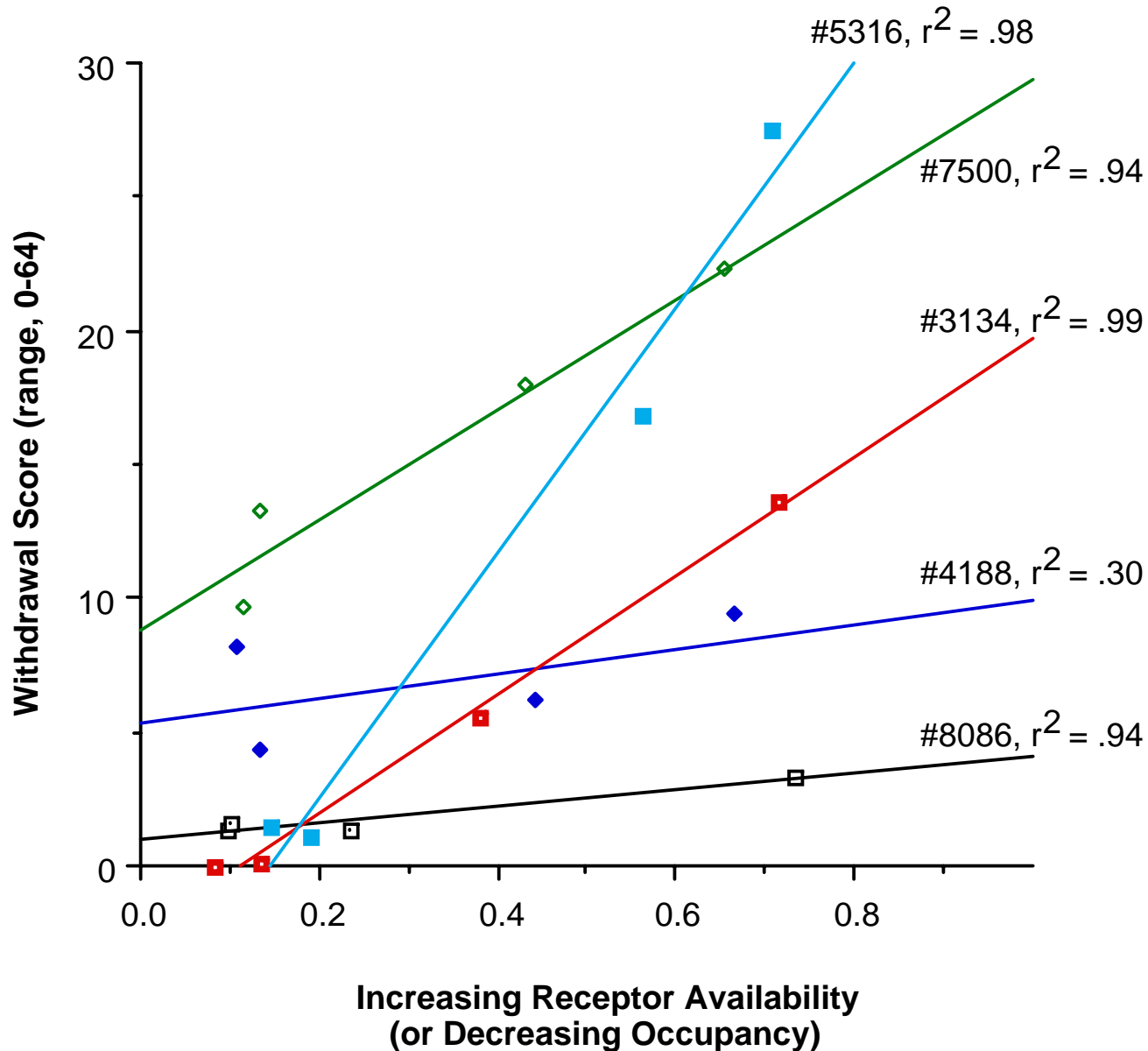


Buprenorphine Plasma Level (ng/ml) 4 hours after daily dose

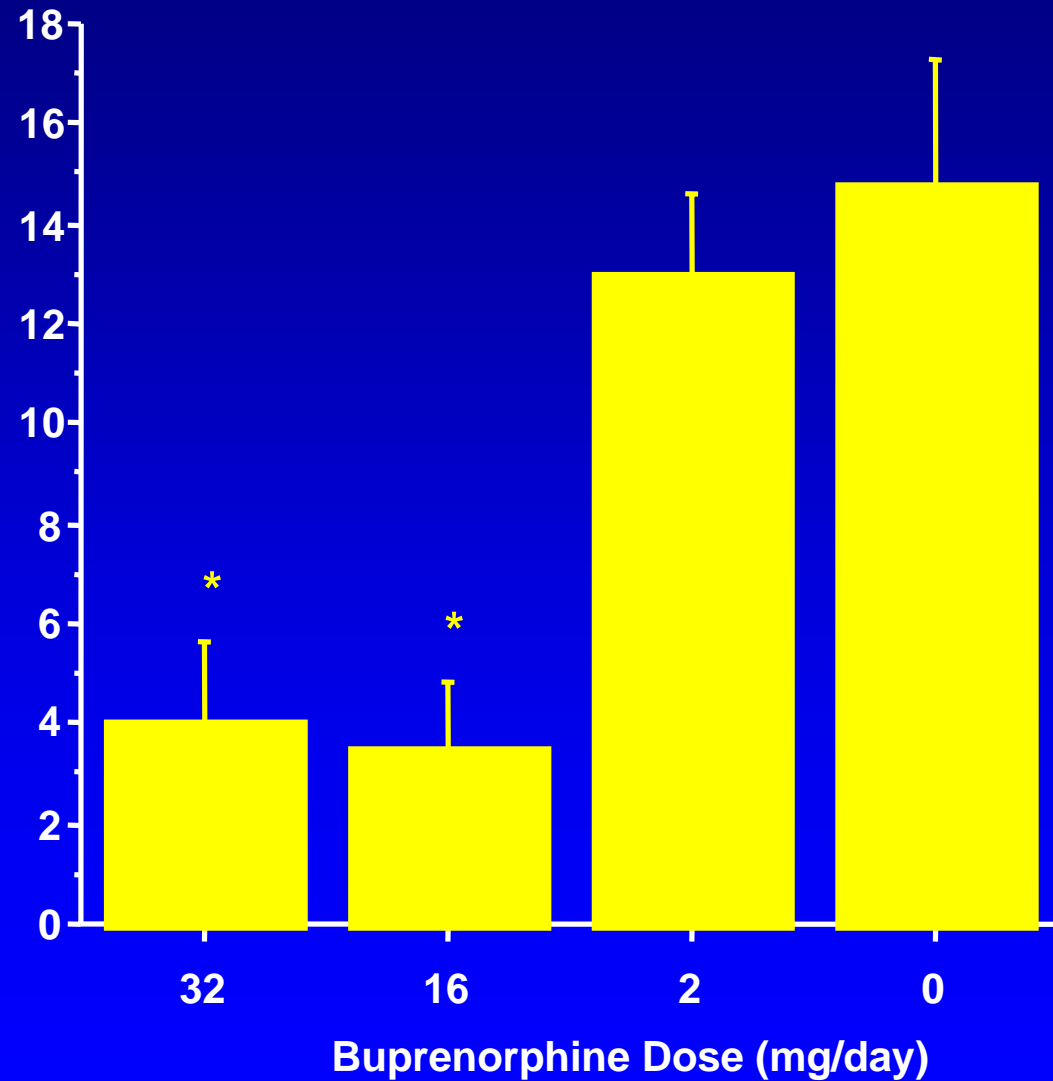
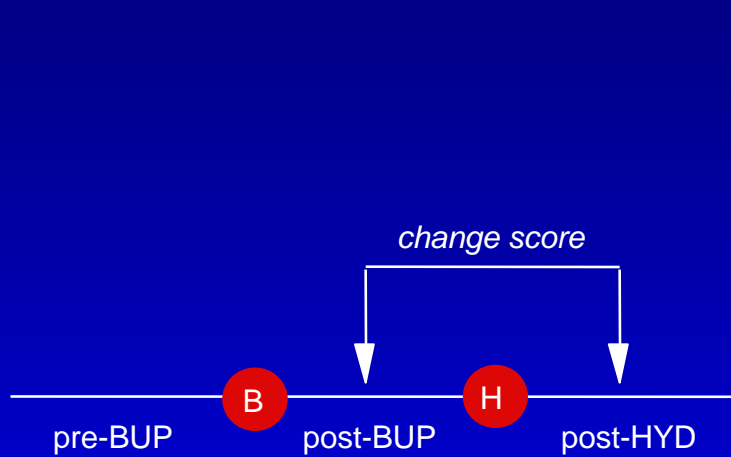


Receptor Availability

μOR Availability vs. Opioid Withdrawal Symptoms



BUP Attenuates Hydromorphone Agonist Symptoms



Study 1 Summary

Decreased μ OR availability (resulting from higher BUP doses) is associated with:

- Higher plasma concentrations
- Less severe opioid withdrawal symptoms
- Less hydromorphone agonist response

Study 2: Vary Time Since Buprenorphine Dose

(Greenwald et al. 2004; in preparation)

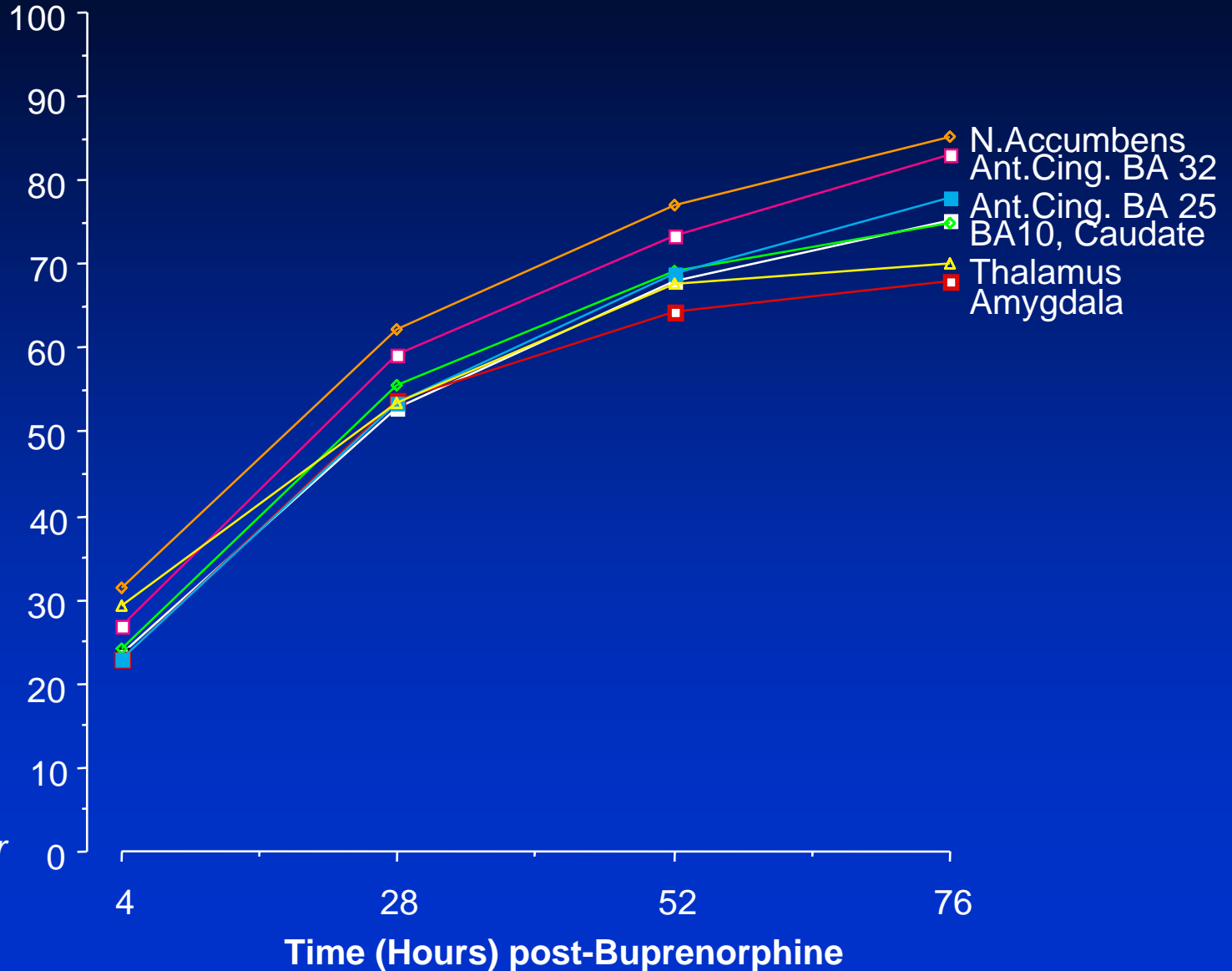
- Determine whether μ OR availability differs at 4, 28, 52 and 76 hrs after omitting the BUP maintenance dose (16 mg)
- Each volunteer was tested in all 4 conditions, thereby serving as his/her own control
- Question: Do post-BUP time-related variations in μ OR availability correlate with BUP plasma levels, opioid withdrawal symptoms, and the ability of BUP to block effects of hydromorphone?

Percent μ OR Availability

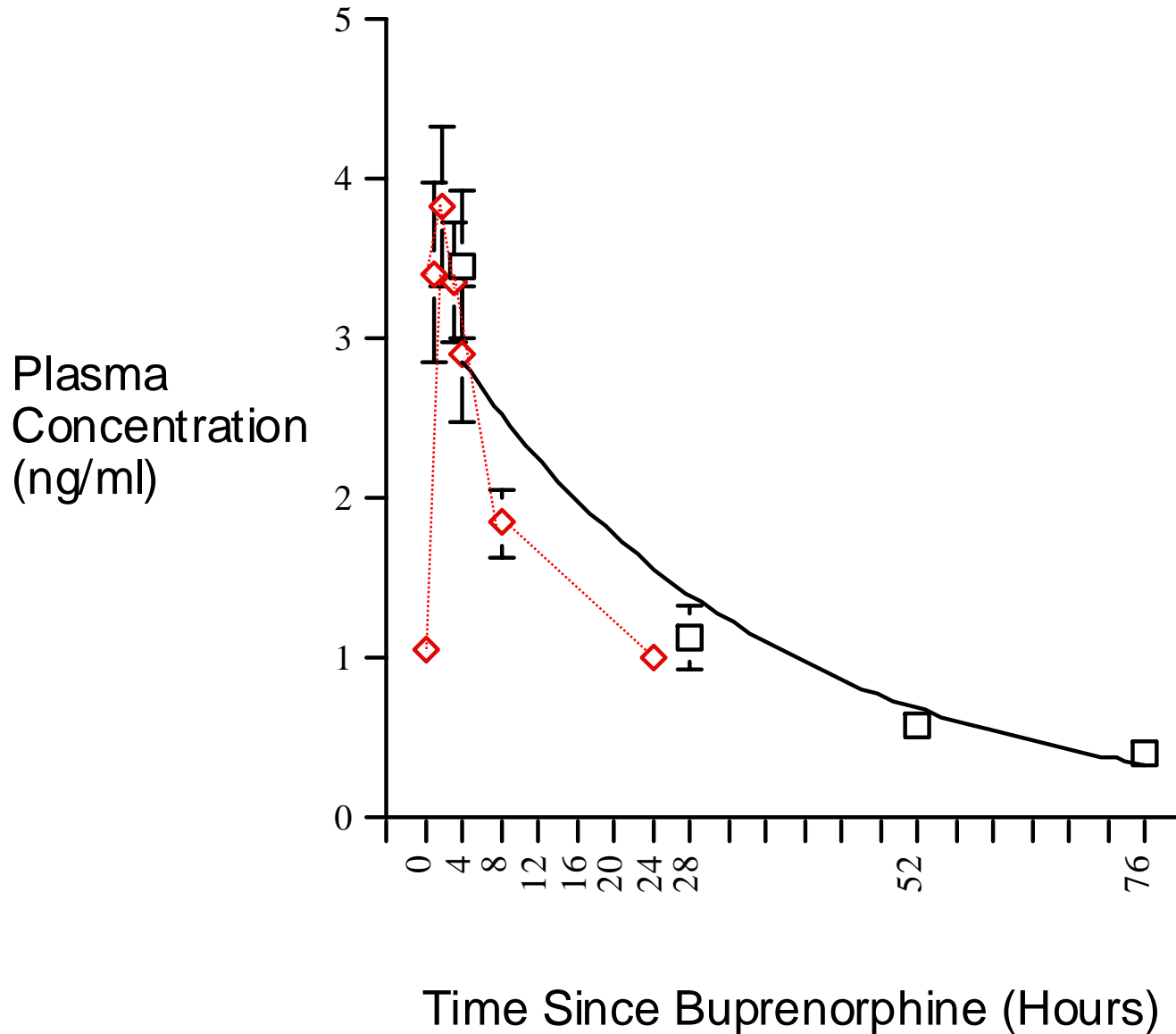
(low receptor occupancy)

Percent Availability of μ ORs

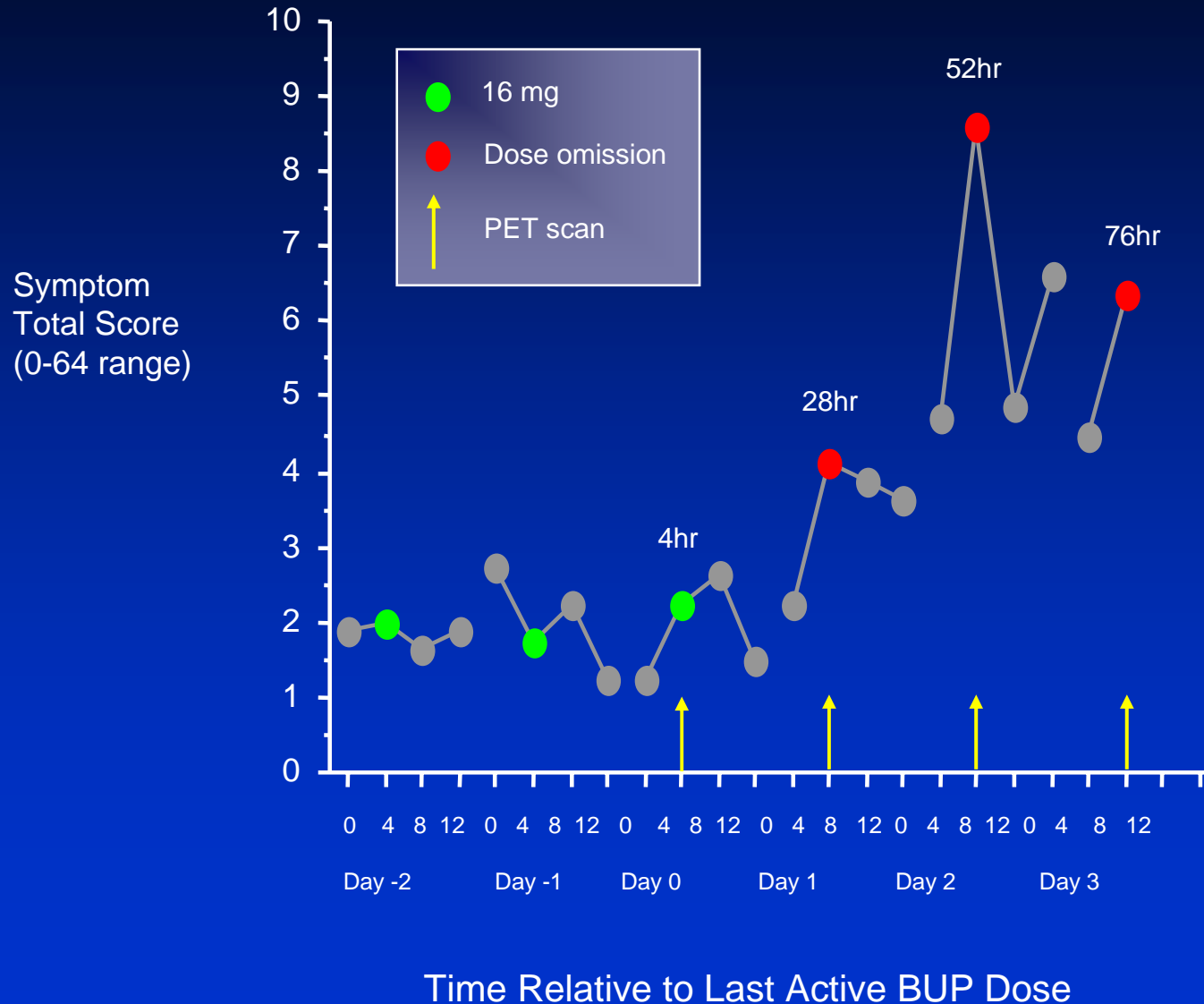
(high receptor occupancy)



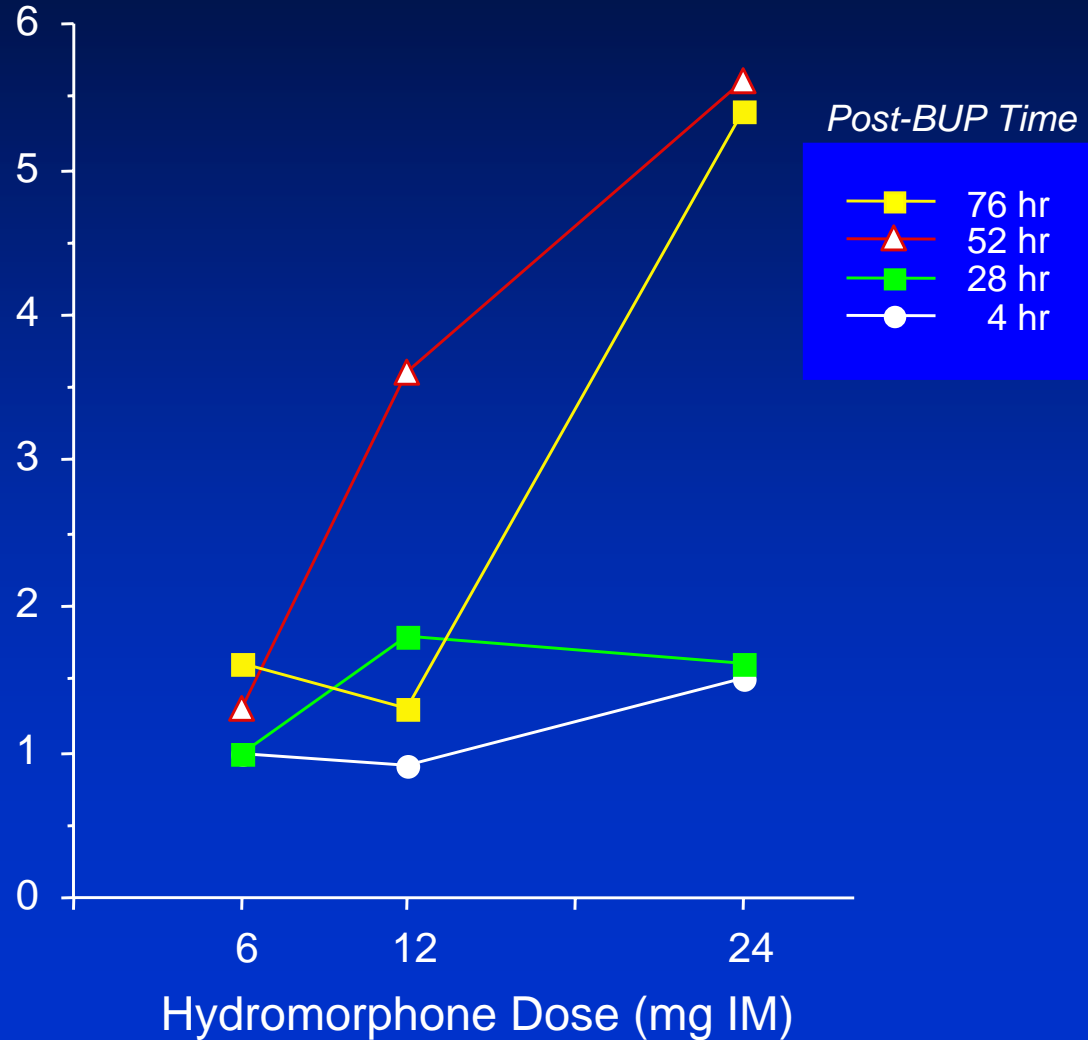
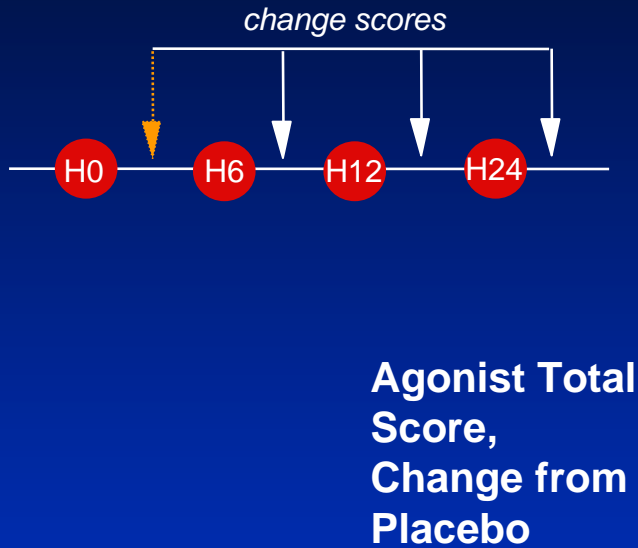
Pharmacokinetics: BUP concentration



Opioid Withdrawal Symptoms



Hydromorphone Agonist Symptoms

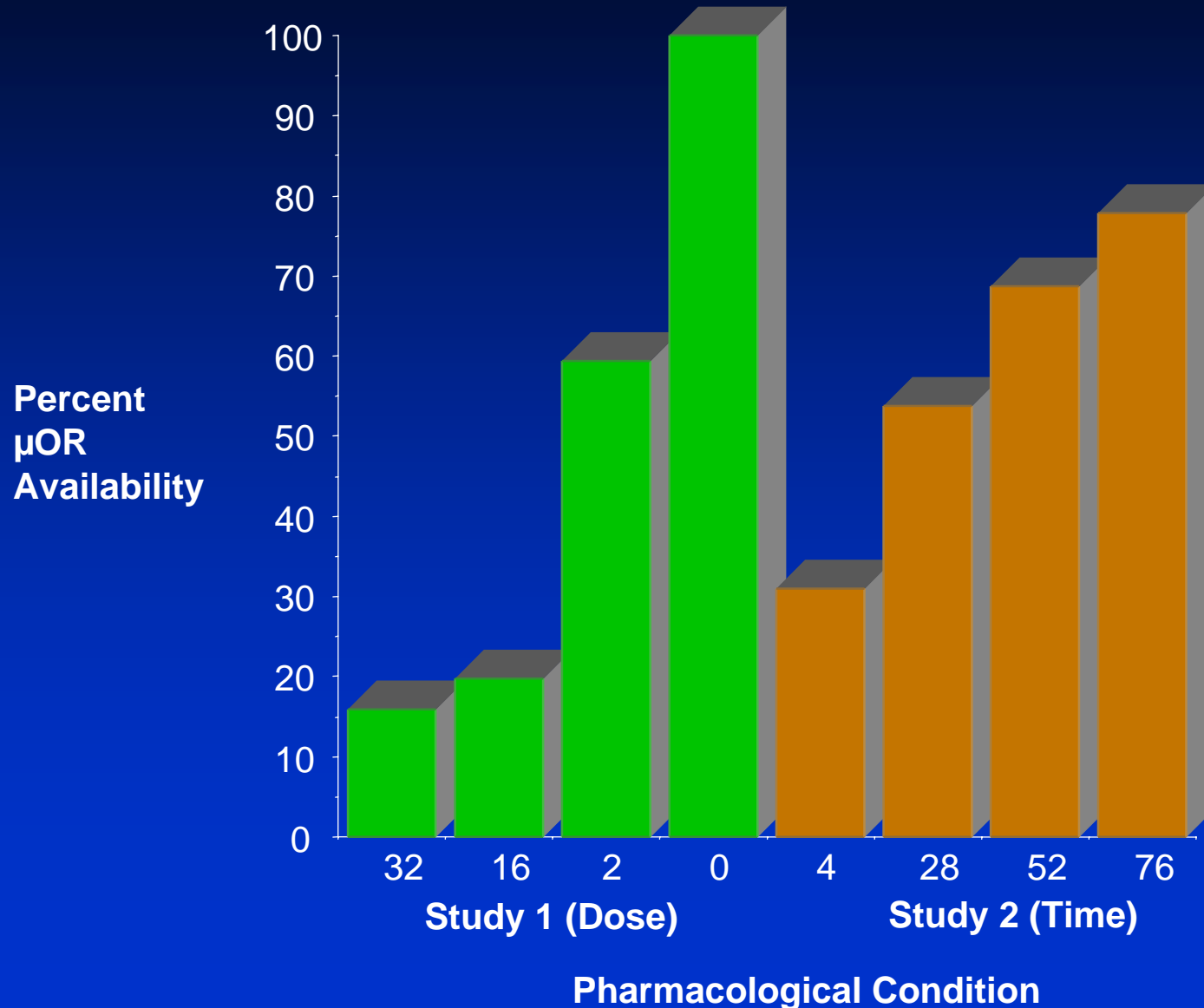


Study 2 Summary

- Placebo substitution for BUP 16 mg over 76 hours produced significant time-dependent:
 - Increases in μ OR availability and withdrawal symptoms, and loss of HYD blockade
 - Decreases in BUP plasma concentrations
 - Substantial correlations among measures
- Relative changes over time
 - Largest changes in plasma levels and withdrawal occurred from 4 hr to 28 hr post-BUP but for blockade the largest change was 28 to 52 hrs
 - Proportionally smaller changes at later time points, with minimal change from 52 hr to 76 hr post-BUP

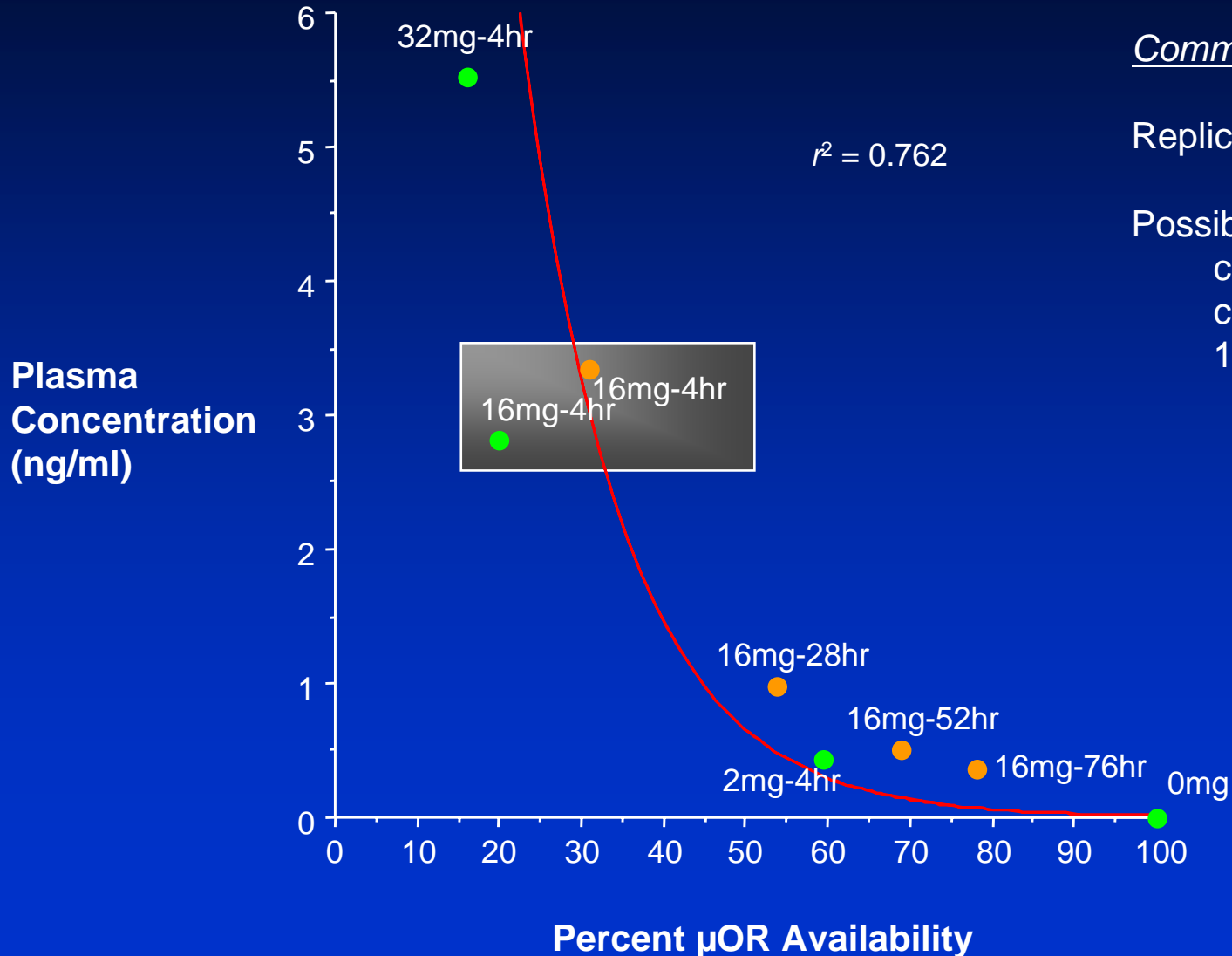
Summary. I

μ OR availability manipulated over a wide range



Summary. II

μ OR availability well correlated with plasma levels



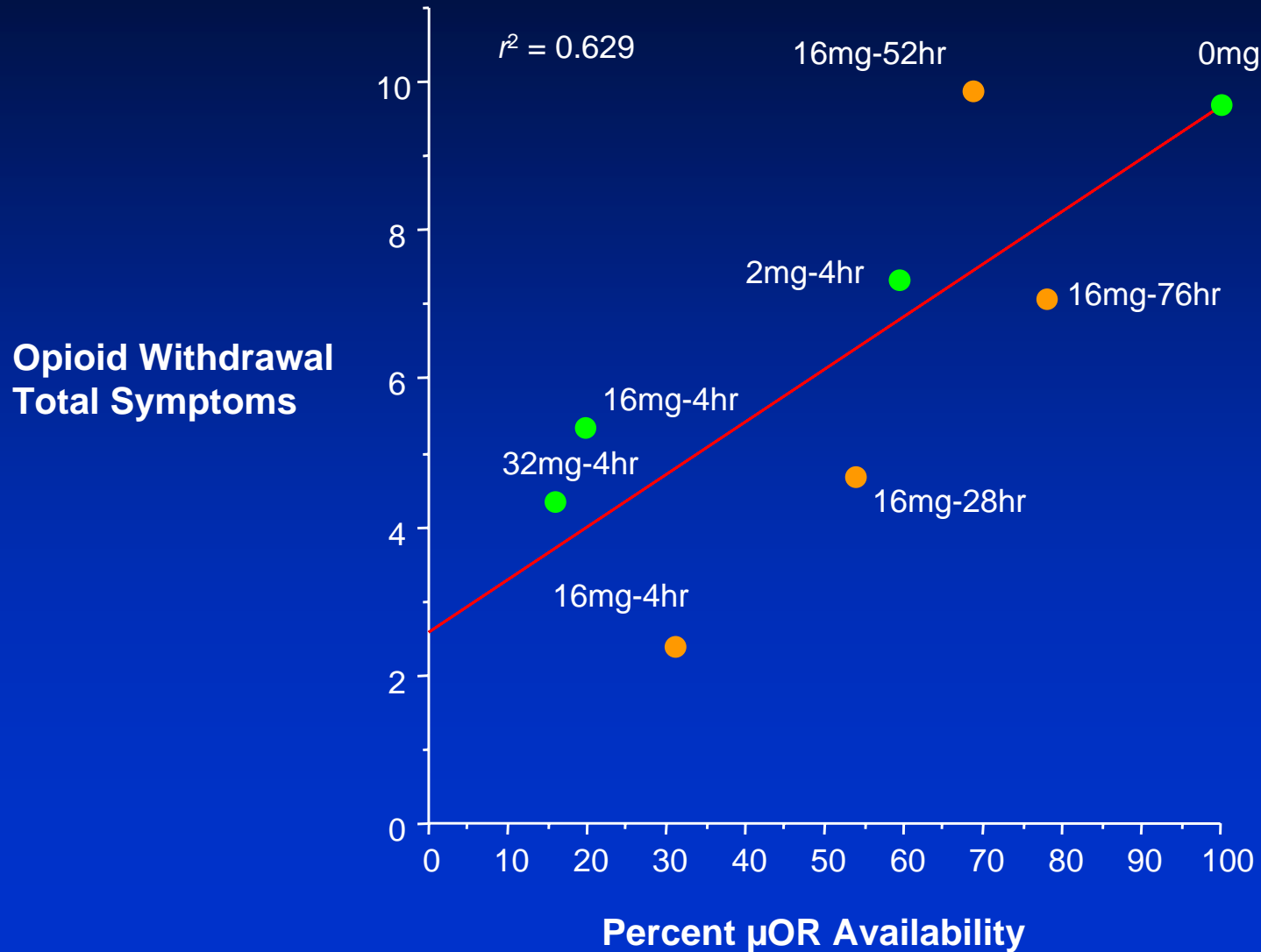
Comments:

Replication of one dose condition

Possible to compare relative concentrations on a single curve, e.g. 2mg-4hr similar to 16mg-52hr

Summary. III

μOR availability related to increased withdrawal



Summary. IV

μ OR availability related to HYD blockade

