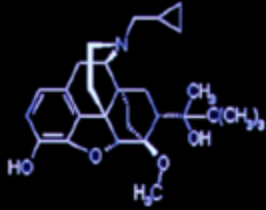
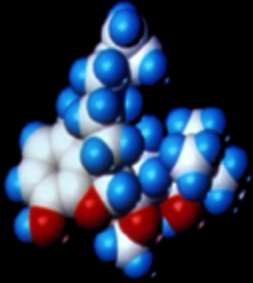


BUPRENORPHINE



Buprenorphine's Efficacy: Lessons from Behavioral Economic Studies

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The presenter declares no financial conflict of interest related to this work

Overview

What I will not cover ...

Cost-effectiveness analysis of BUP treatment
(tomorrow afternoon)

What I will cover ...

Clinical studies of behavioral economic parameters
that may influence BUP efficacy

- Pharmacological factors
 - Unit price of self-administered (illegal) drug
 - Agonist drug supply
- Non-pharmacological factors
 - Non-drug reinforcement
 - Individual differences

Medication Development: Some Rules of Thumb

Axiom 1

Behaviors – especially drug seeking/use – are complexly determined

Axiom 2

No medication is a magic bullet

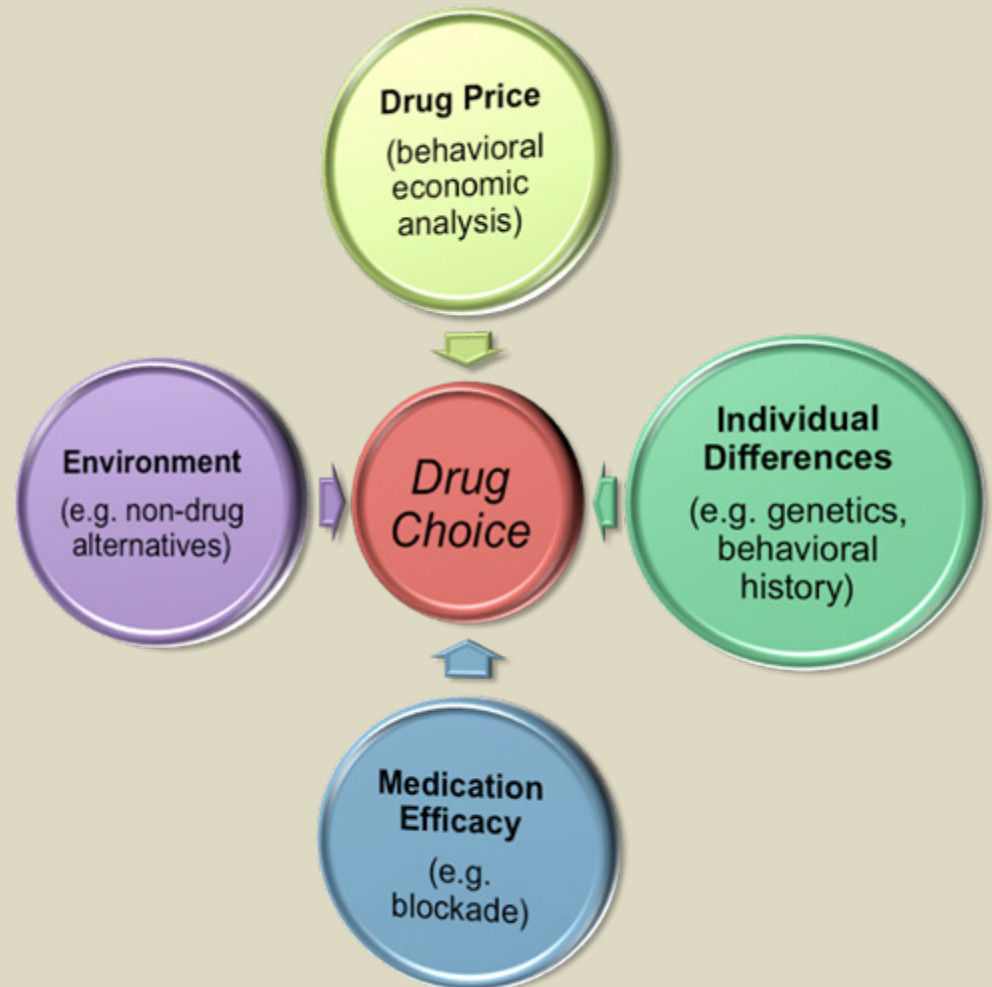
Axiom 3

Critical to focus on *non-pharmacological* factors that can enhance the efficacy of medications

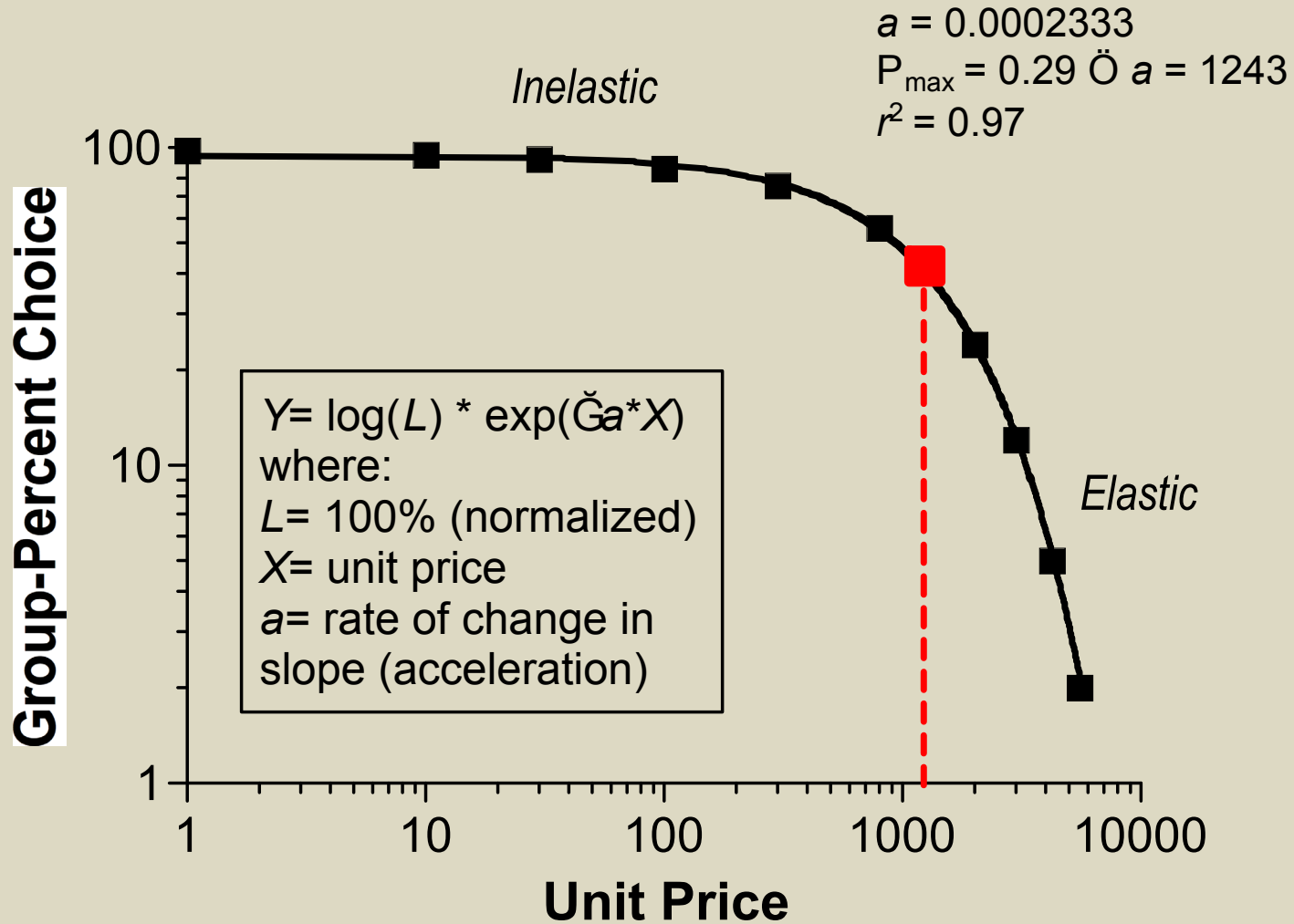
Reducing drug choice/demand is primary target: Must consider multiple influences

Drug choice paradigms incorporate many useful features for medication development

- ✓ Dose-dependent effects (of medication and abused drug)
- ✓ Non-drug environmental alternatives (analog behavior therapy)
- ✓ Choice procedures can be integrated with progressive ratio schedules to vary drug 'price', which can be converted into behavioral economic analyses
- ✓ Incorporate the study of individual differences



Behavioral Economic Analysis Primer



(UP = cost ÷ benefit = response requirement ÷ dose)

Buprenorphine Demand is Inelastic

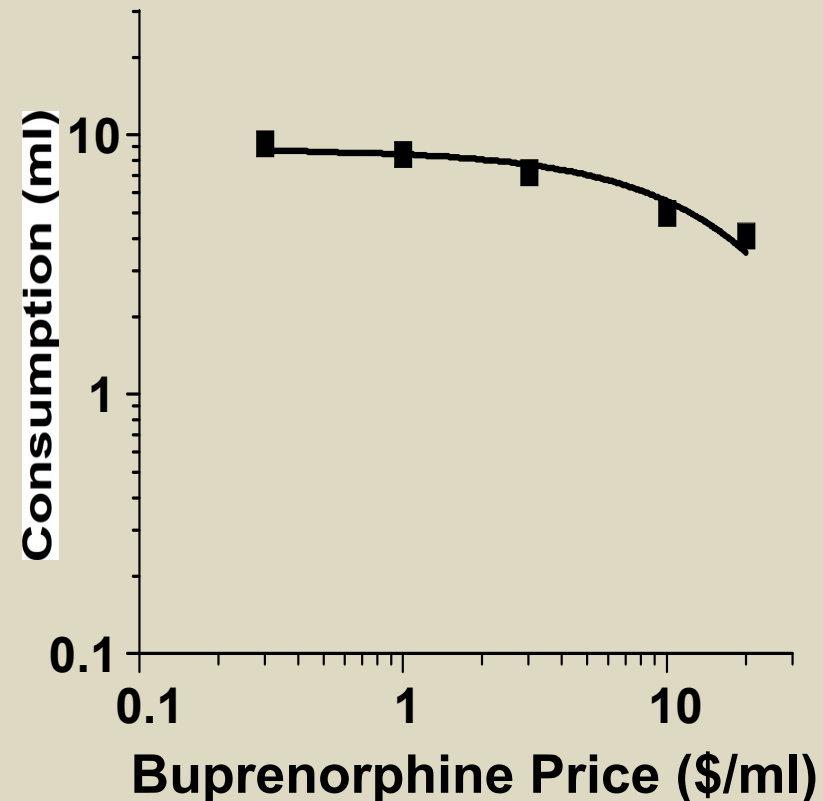
Adapted from Petry and Bickel (1999)

Participants. 8 heroin-dependent outpatients were maintained on BUP 8 mg/day ($n=3$) or 16 mg/day ($n=5$), and required to be drug-abstinent.

Methods. On experimental days, the BUP dose was response-contingent in a closed economy (i.e. no other BUP beyond what they chose). Patients could choose 10x between BUP s.l. liquid dose units (each 1/5th of the maintenance dose) and different money amounts (\$0.30, \$1, \$3, \$10 and \$20).

Results. At low BUP unit prices (money alternative amounts), patients chose BUP exclusively. As BUP price increased, patients selected modestly lower daily BUP doses. Demand for BUP was inelastic (point-to-point slope values > -1).

Conclusion. BUP-maintained patients did not readily forego their daily dose.



Buprenorphine Demand: Open Questions

- (1) Is an individual's medication demand (e.g. measured with actual choice methods, or simulated procedures such as "willingness to pay") predict retention and/or illegal opioid use during treatment?
- (2) Is BUP demand elasticity a function of between-subject differences in pharmacodynamics (e.g. opioid dependence severity, pain) or pharmacokinetics (e.g. SNPs that alter metabolism)?
- (3) Further studies would be useful re: the *personal* cost (unit price) of BUP and its deterrent effect on treatment retention and drug use. However, personal cost is independent of provider cost.

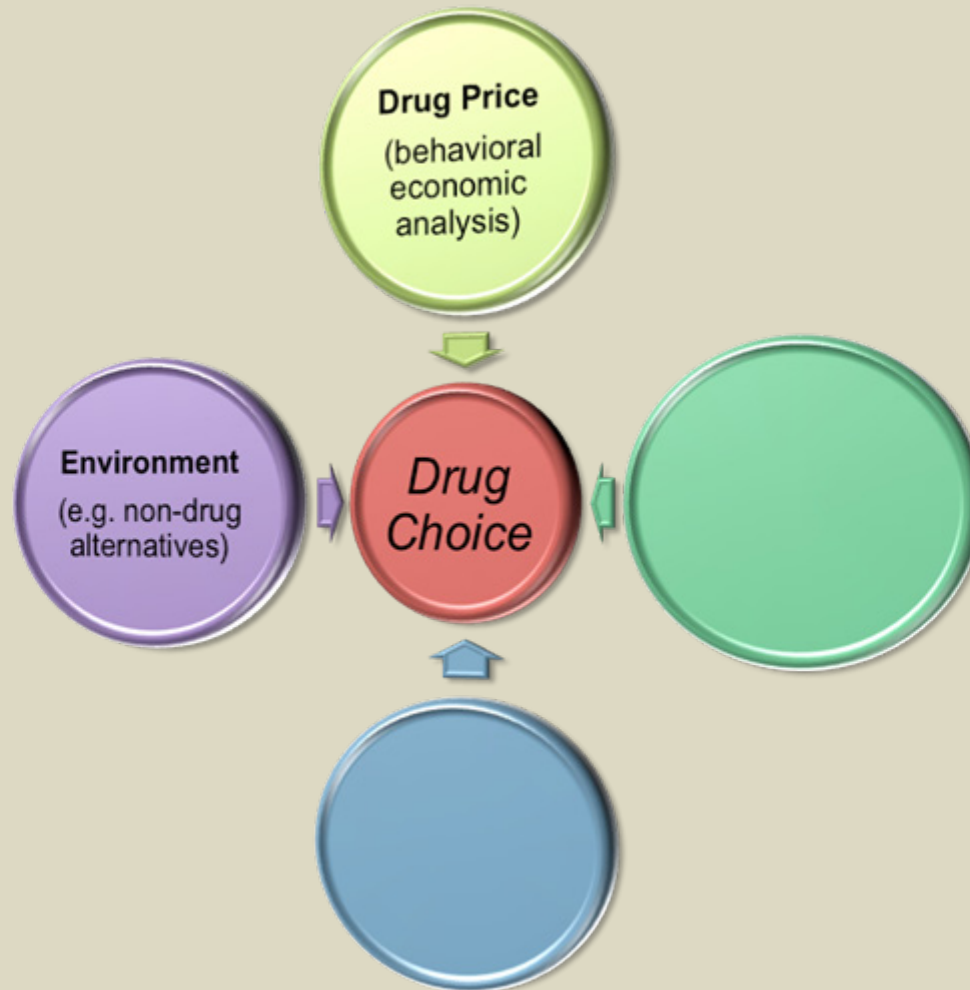
Comparative Treatment Costs (\$) Over 6 Months

(Jones et al. 2009)

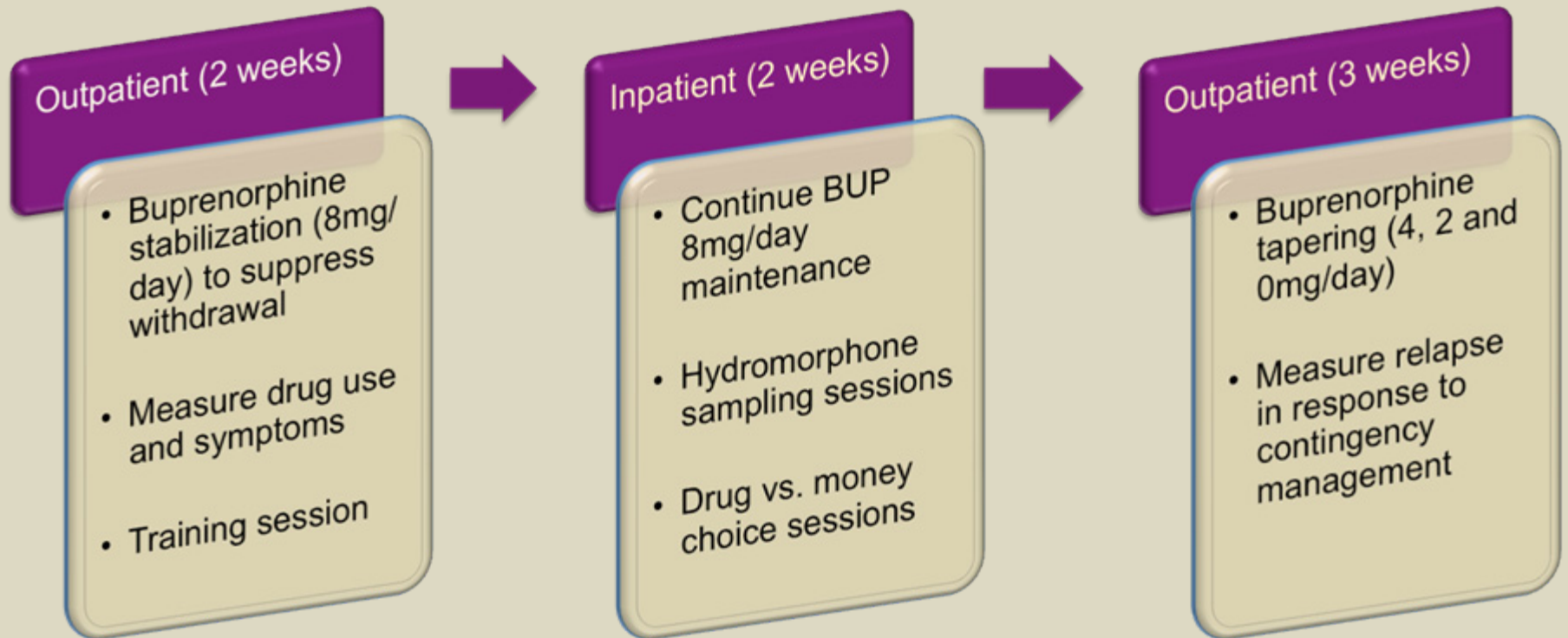
	Methadone Clinic (n=23)		Methadone Office (n=21)		Buprenorphine Office (n=34)	
	Low UP	High UP	Low UP	High UP	Low UP	High UP
Provider Cost	117	183	149	279	292	499
Patient Cost	84	133	55	105	34	65

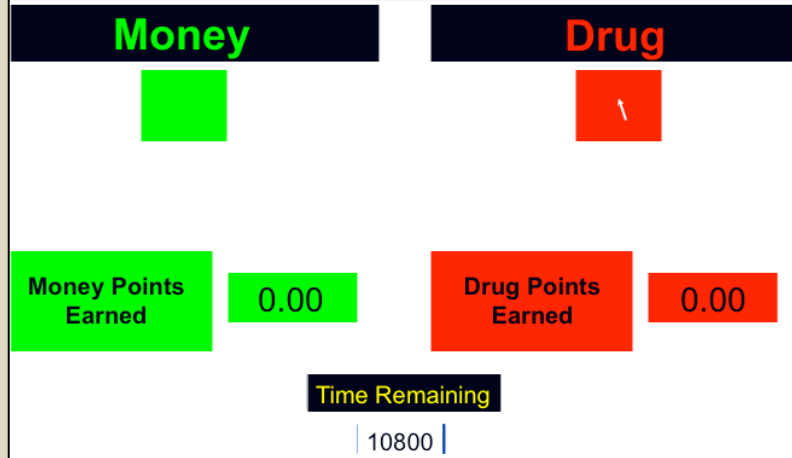
No significant group differences in treatment benefit (83-91% treatment retention and 75-86% drug abstinence), thus costs shown in table are proportional to unit price.

Non-Pharmacological Factors Significantly Moderate Buprenorphine's Efficacy



General Methods: Protocol Timeline





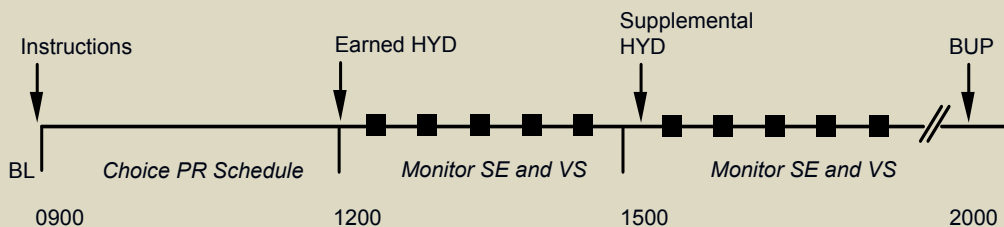
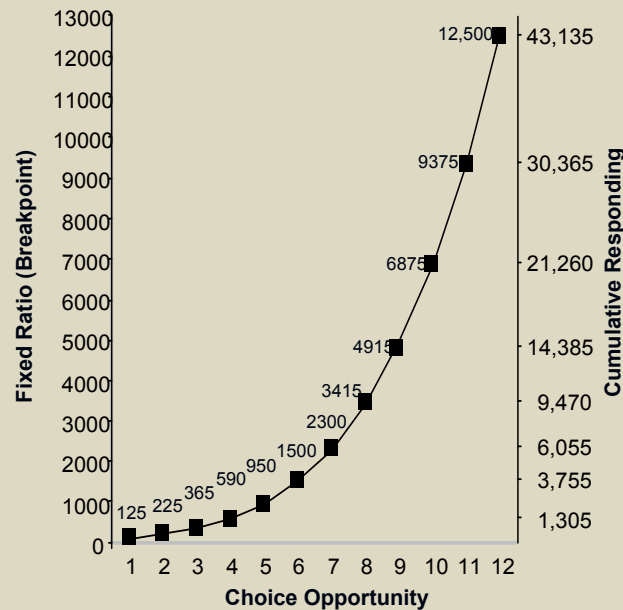
Choice Progressive Ratio Schedule of Reinforcement

12 choice opportunities/session

- Exponential response requirements
- On each trial, subject could choose between:
 - Unit HYD dose (2 mg)
 - Money alternative (\$2 or \$4)
 - Few alternatives (water and bathroom break only; no smoking or activities)

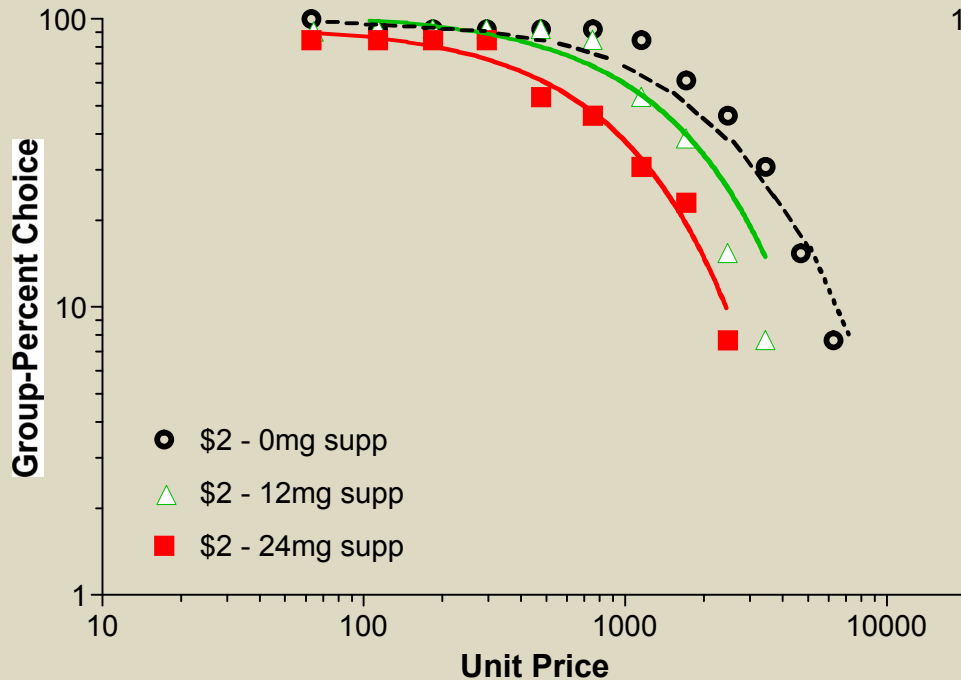
Delivery of reinforcement

- Total earned dose given after 3-hour session
 - *Paradigm measures drug seeking, not confounded by interim drug deliveries*
- Total earned money paid on morning of discharge (delayed reinforcement)

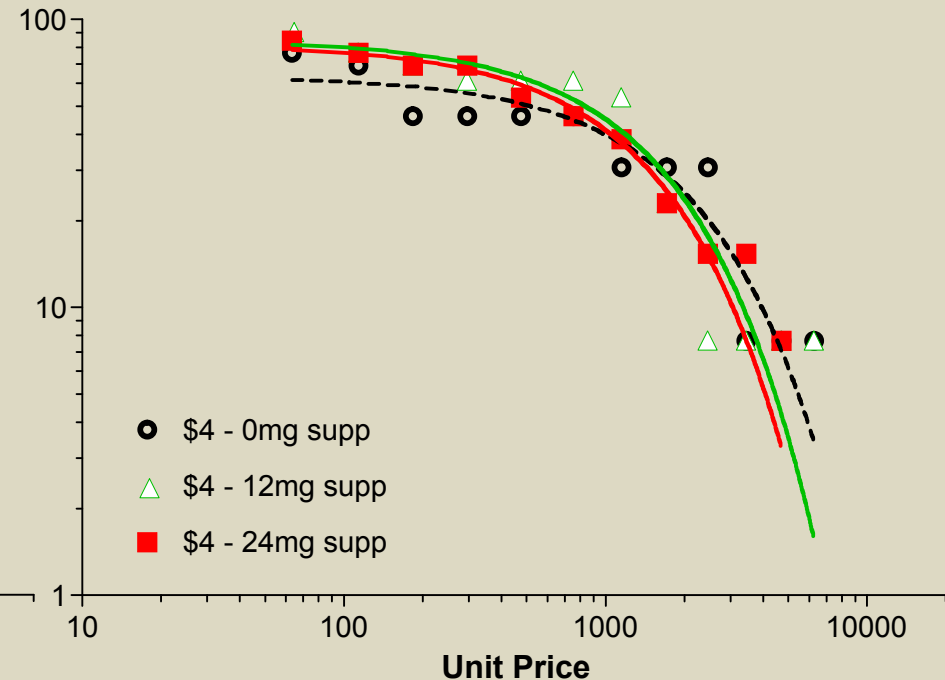


During BUP 8-mg/day maintenance, money alternative amount (*analog*= CM voucher magnitude) and extra agonist supply (*analog*= free take-home dose) influence demand

Low-Magnitude Alternative



High-Magnitude Alternative



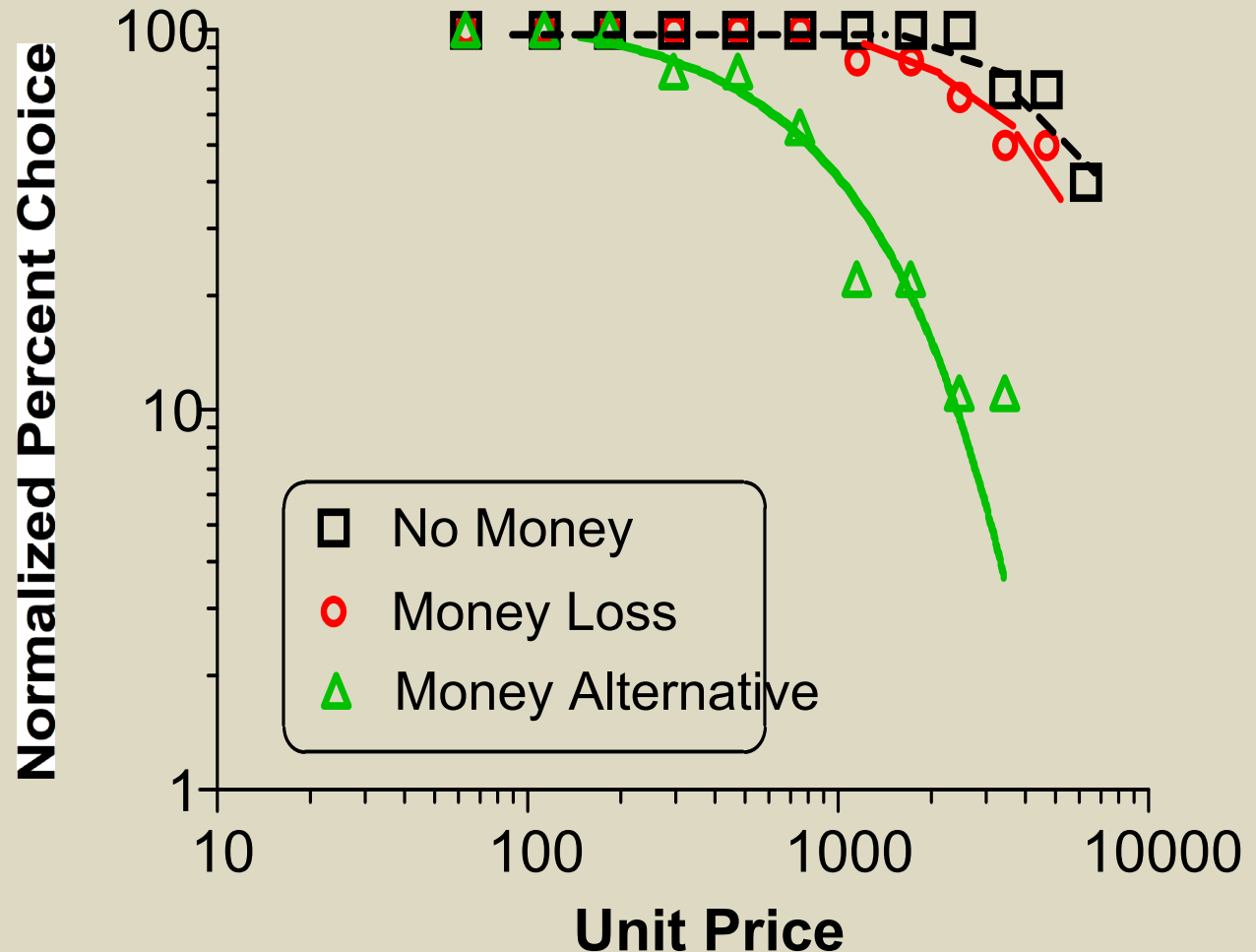
- > Without agonist supplement, opioid demand more elastic with high vs. low-magnitude alternative ($P_{max} = 1650$ vs. 2886; compare black dashed curves across panels).
- > With the less effective lower-magnitude alternative, extra agonist supply increases elasticity.
- > With the more effective higher-magnitude alternative, extra agonist supply has minimal effect.

During BUP 8-mg/day maintenance, opioid demand is more elastic with positive reinforcement than punishment

(Greenwald, in press, *Drug Alcohol Depend*)

Subjects earned daily wage of \$40. During experimental sessions, could work for HYD unit doses under 3 different conditions:

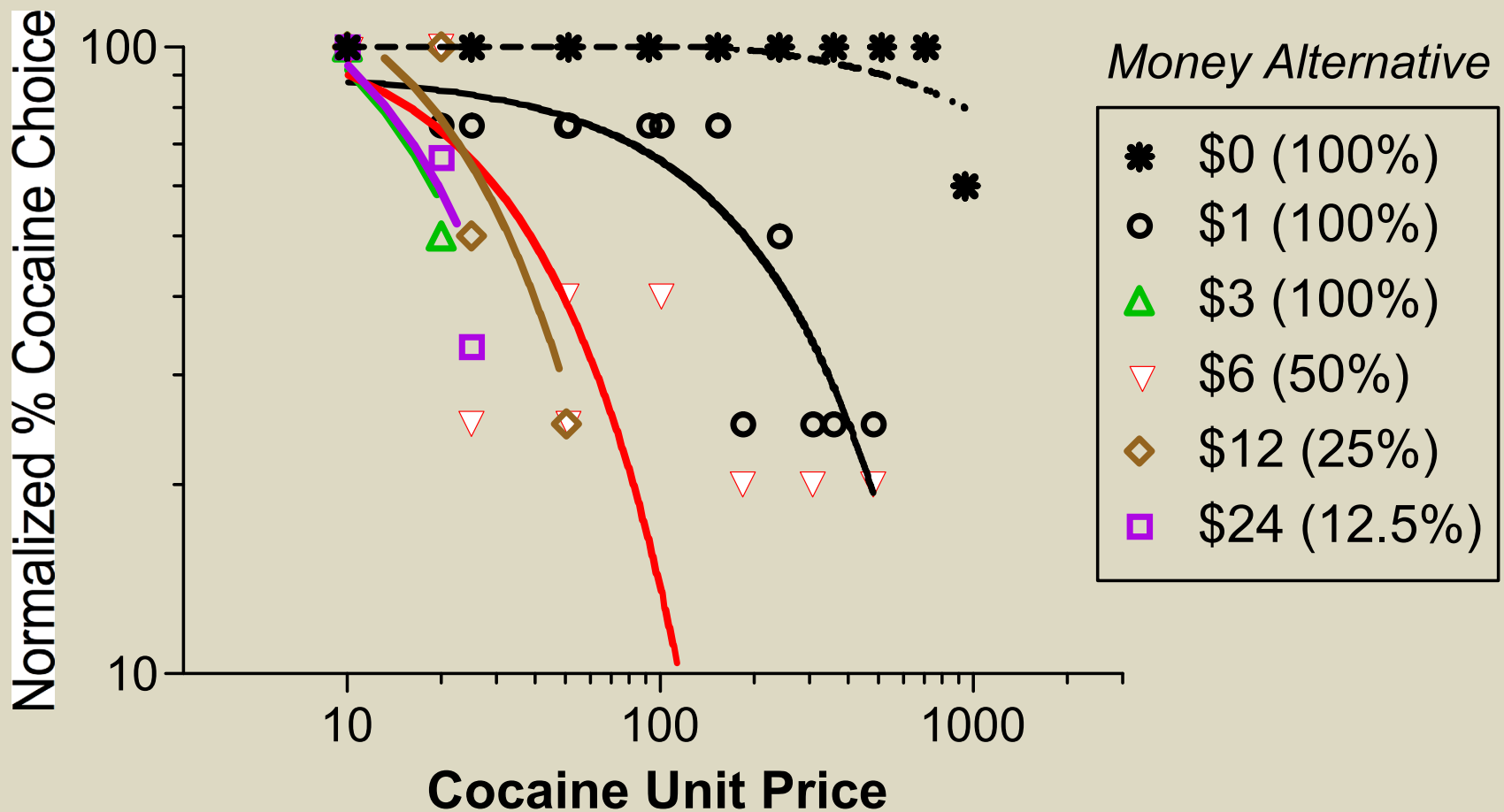
- No money: only drug choice was available
- Money loss: only drug was available, plus lost \$4 for every drug choice
- Money alternative: both options available; gained \$4 when they chose money instead of drug



Optimizing non-drug reinforcement:

Expected utility may mediate increased cocaine demand elasticity
(Greenwald et al., study in progress)

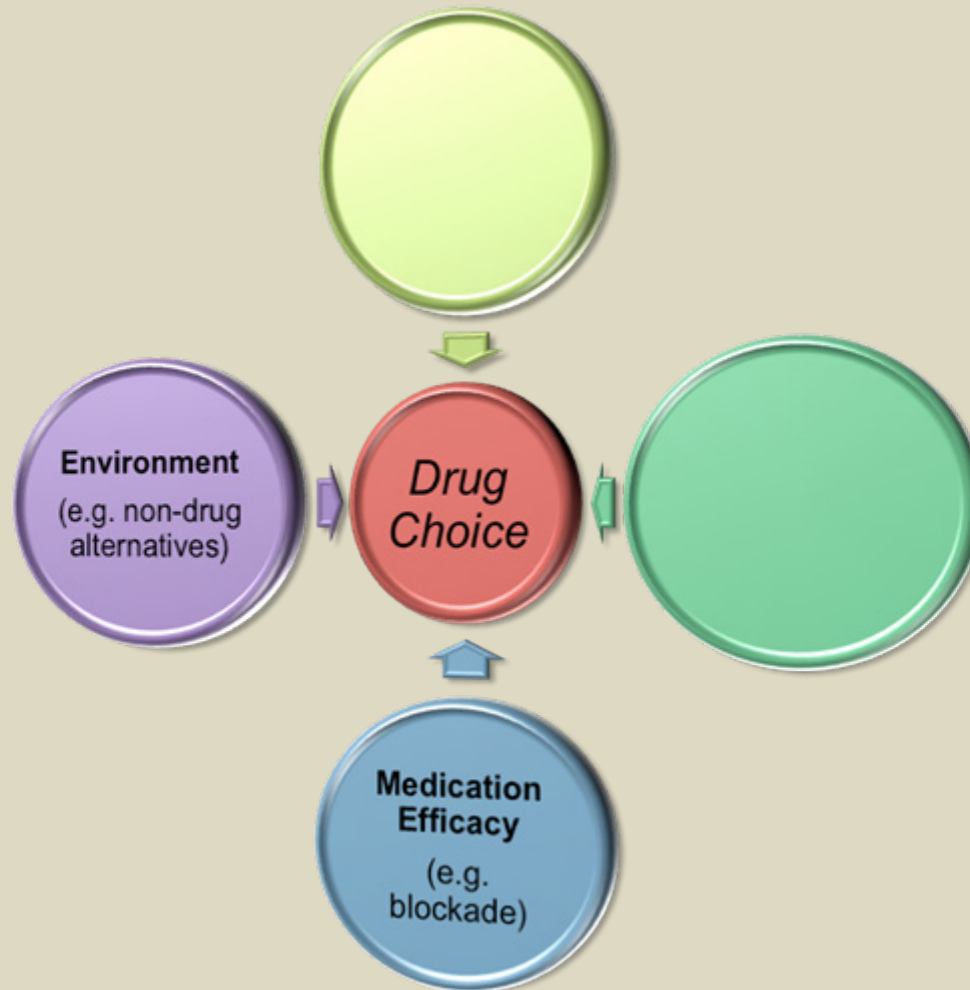
The data presented on this slide is from a study currently in progress and should not be cited



Environmental Factors: Open Questions

- (1) Is BUP efficacy limited for individuals with extensive illegal drug supply (availability)?
- (2) To what extent does prize CM, relative to standard escalating CM, enhance BUP efficacy?
- (3) In individuals for whom BUP + non-pharmacological reinforcement does *not* reduce drug demand, what are the next most effective environmental manipulations/therapies that can be tried to reduce demand?
- (4) Are punishment procedures generally less effective or can they be effective in sub-populations (e.g. criminal justice)?

Medication x Non-drug alternative interaction effects on drug demand



Buprenorphine + Contingency Management

-> *Escalating CM can maintain abstinence once established, but subsequently increasing the price of abstinence erodes efficacy*

“Upping the ante” can backfire: Escalating CM + BUP + desipramine maintained opioid and cocaine abstinence. After eliminating 'escalating CM', BUP+DMI maintained drug abstinence. However, increasing voucher contingency requirement led to increased drug use (Kosten et al. 2003)

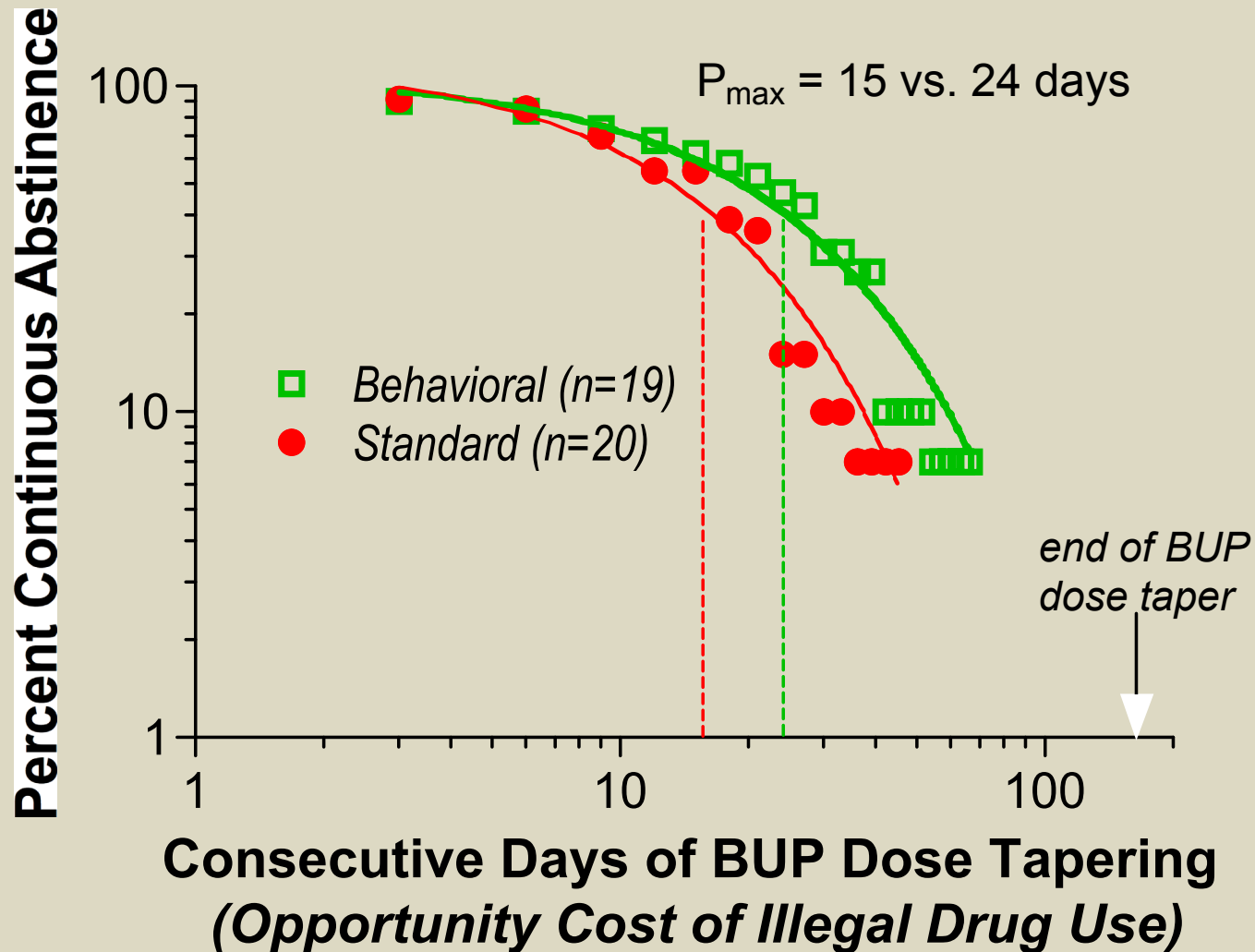
-> *Abstinent-contingent BUP (increasing BUP price) can be effective for increasing drug abstinence but not necessarily retention, and has potential to be more cost-effective than voucher reinforcement*

“Half and half” can work well: Patients earned 1/2 the thrice-weekly dose for clinic attendance and other 1/2 dose for opiate + cocaine abstinence over 12 weeks. This contingency produced twice the duration of continuous abstinence than a low-cost escalating voucher reinforcement group or standard treatment group (Gross et al. 2006)

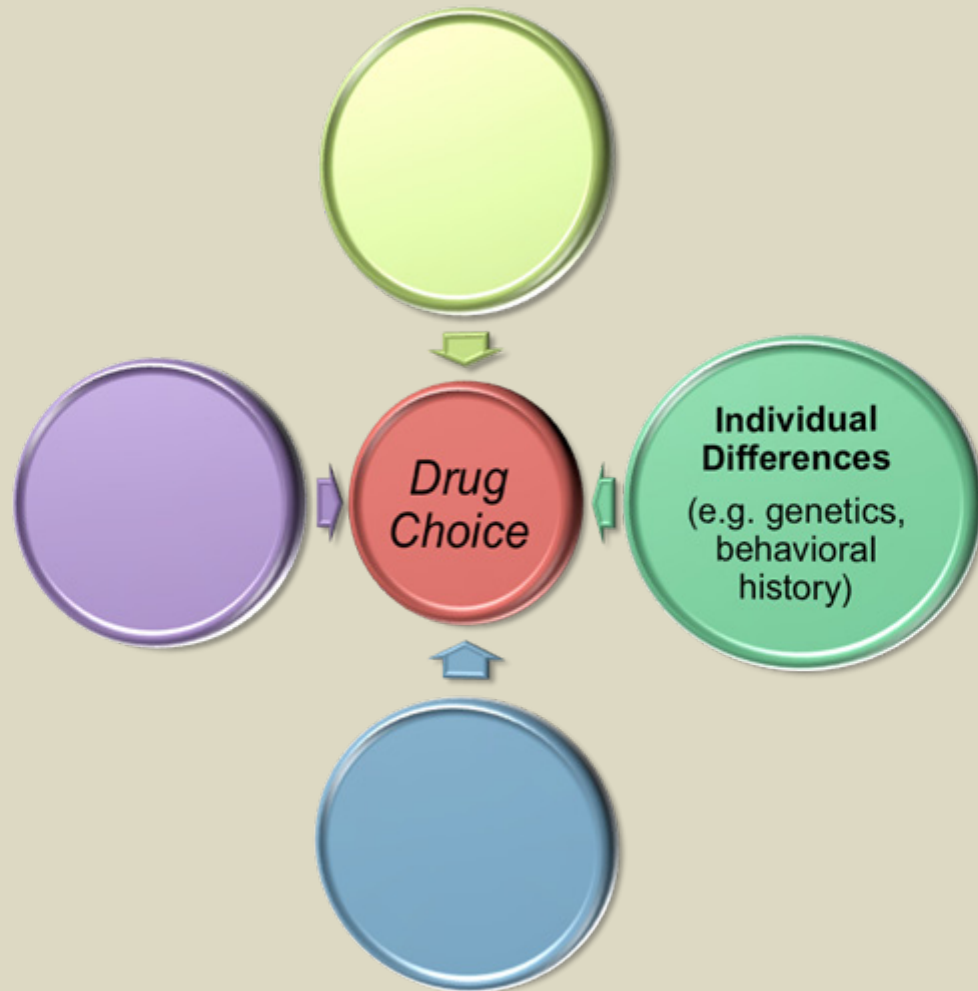
Losing privileges (negative punishment) has mixed effects; “separates men from boys”: Patients dosed 3x weekly if opioid- and cocaine-abstinent, otherwise they had to attend clinic daily and received a one-day 50% dose reduction if drug positive. Over 12 weeks this reduced drug – mostly opioid – use (had the same efficacy as abstinence voucher reinforcement group) compared to controls, but also increased attrition relative to the voucher group (Chopra et al. 2009)

Behavioral Treatment Helps Opioid Dependent Patients “Defend Abstinence” During BUP Dose Tapering

Adapted from Bickel et al. (1997)

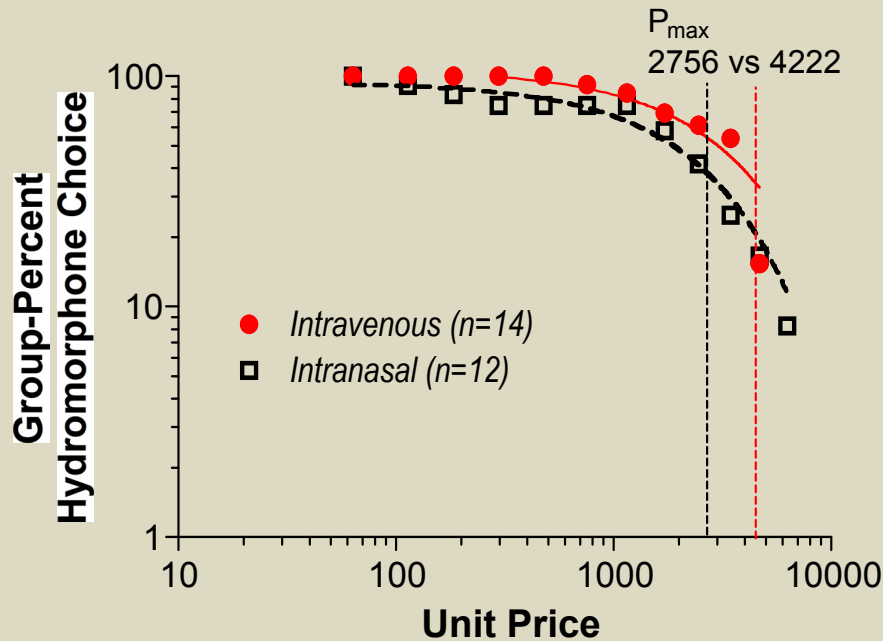


Individual differences in drug demand

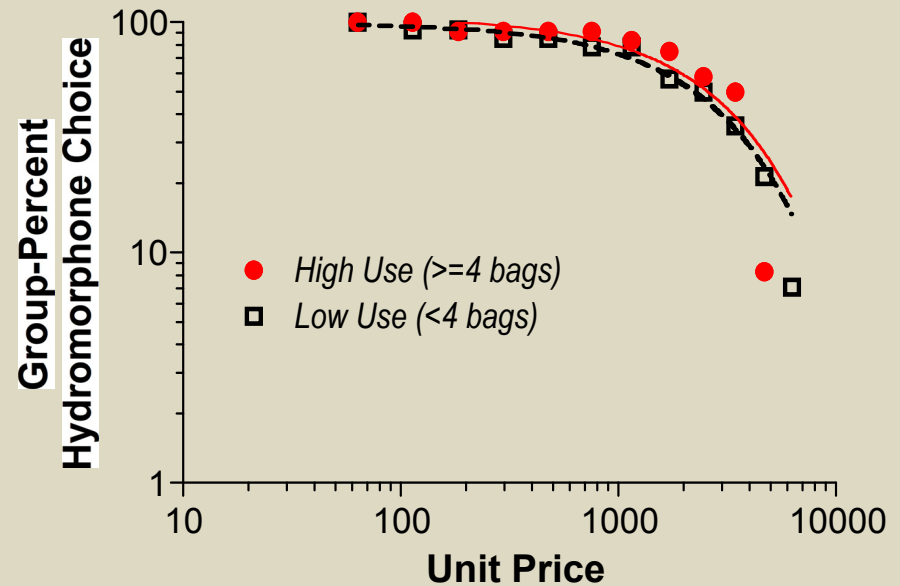


During BUP 8mg/day Maintenance, Opioid Demand is...

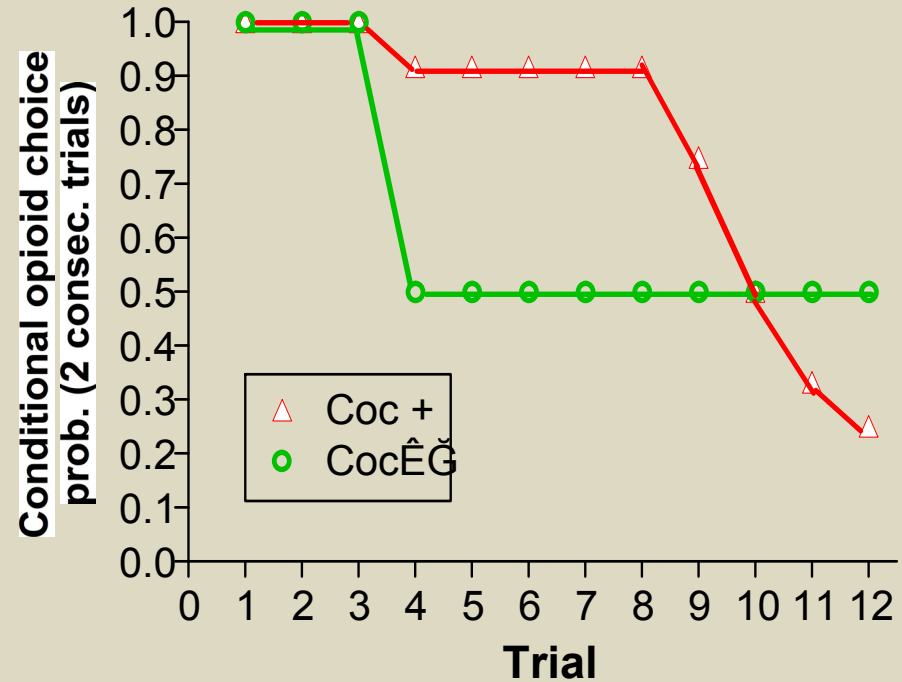
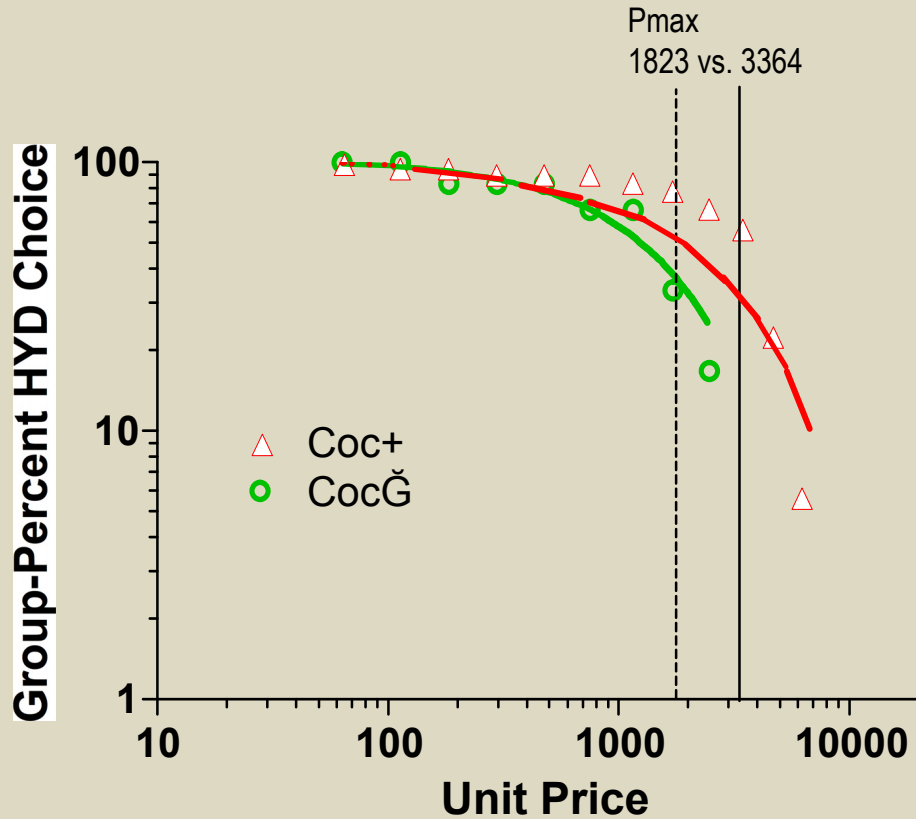
Significantly More Inelastic Among IV vs. Intranasal Heroin Users



Similar for Heavier vs. Lighter Heroin Consumers



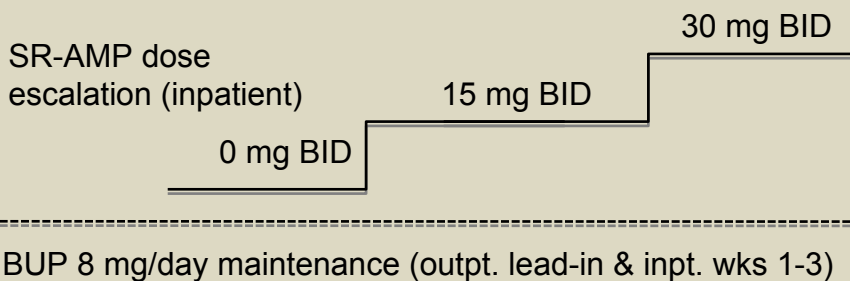
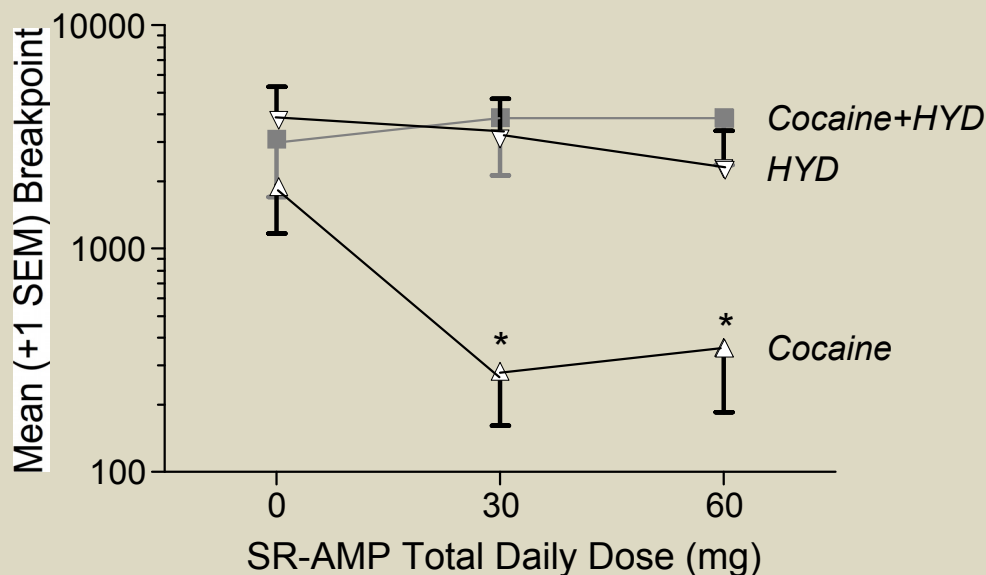
During BUP Maintenance, Recent Cocaine Users Exhibit More Inelastic Opioid Demand: Prices and Conditional Probabilities



Opioid/Cocaine Dual Agonist Pharmacotherapy Model:

Sustained release *d*-amphetamine (SR-AMP) during BUP stabilization decreases cocaine but not 'speedball' breakpoints in cocaine/heroin-dependent volunteers

Greenwald et al., manuscript in preparation



Within-subject, double-blind design

- Amphetamine dose (3 levels): Ascending, each dose for one week; capsules administered at 7:00 AM and 12:30 PM each day
- Drug options (4): Randomized crossover, double dummy (intranasal and intramuscular)

Three full days stabilization (Sat-Mon) on each SR-AMP dose, followed by 4 consecutive days of sessions (Tue-Fri)

Morning (9 AM – noon): Sample drug combo

- Cocaine (100 mg IN), HYD (24 mg), Cocaine+HYD ('speedball'), and dual placebo

Afternoon (12:30 – 3:30 PM): Series of 12 PR

- choices between units of the drug combo and money (\$2.00), with total response-contingent amount delivered at the end of the 3-hr session
- Cocaine unit dose = 8mg IN (max = 100 mg)
- HYD unit dose = 2mg IM (max = 24 mg)

Lessons Learned. 1

BUP demand appears to be inelastic in BUP-maintained individuals, which may predict its adherence and ability to reduce drug use – at least for some patients.

BUP is an effective reinforcer – i.e. withholding its delivery, contingent on attendance or drug abstinence, can increase adherence. Because BUP is intrinsic to treatment, it can be used cost-effectively (in combination with other therapies).

Caveats:

1. Administering BUP contingently (based on abstinence) increases its unit price and potentially its elasticity, leading to reduction in self-administration (increased attrition).
2. Not clear whether BUP demand is similarly inelastic across a wide range of individuals, e.g. those who are severely dependent, or new to treatment.
3. Must be careful in these experimental analyses to distinguish impact of individuals' vs. providers' BUP unit price on its ability to promote adherence and abstinence

Lessons Learned. 2

Non-pharmacological reinforcement, in combination with BUP, is critical for reducing drug demand, and deserves to be used more creatively.

1. Positive reinforcement has magnitude-dependent effects on opioid demand elasticity. This is consistent with the efficacy of escalating voucher-based reinforcement, but also other techniques that enhance non-drug activities.
2. Positive reinforcement may increase opioid demand elasticity more than punishment in most contexts. But more studies are needed, particularly in settings where punishment holds sway (criminal justice). Punishment is not incompatible with positive reinforcement (think: *reset contingency* during CM), but may erode retention.
3. Expected utility may underlie ability of non-pharmacological reinforcement to increase drug demand elasticity.
 - > Could constructing individual-patient utility curves form a basis for tailoring treatment? Could behavioral economic counseling be incorporated into standard psycho-educational approaches?

Lessons Learned. 3

Buprenorphine is generally less effective among opioid-dependent cocaine abusers than non-cocaine users.

This problem is not unique to BUP (also presents a challenge with MMT)

Opioid dependent, BUP-maintained individuals who also use cocaine exhibit:

1. greater *opioid* demand inelasticity in the laboratory (cross-sensitization)
2. have lower drug abstinence rates during clinical trials involving opioid maintenance
3. appear to relapse more quickly during BUP dose tapering

Non-pharmacological reinforcement (e.g. CM) and dual-agonist medication (e.g. BUP + *d*-amphetamine) may decrease cocaine demand, which otherwise complicates opioid dependence treatment with BUP

Gracious Thanks to ...

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