

Abuse Liability of Maintenance Medications for Opioid Dependence

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THS Conference
Biarritz, France
15 October 2009

RATIONALE

Buprenorphine is an effective treatment for opioid dependence

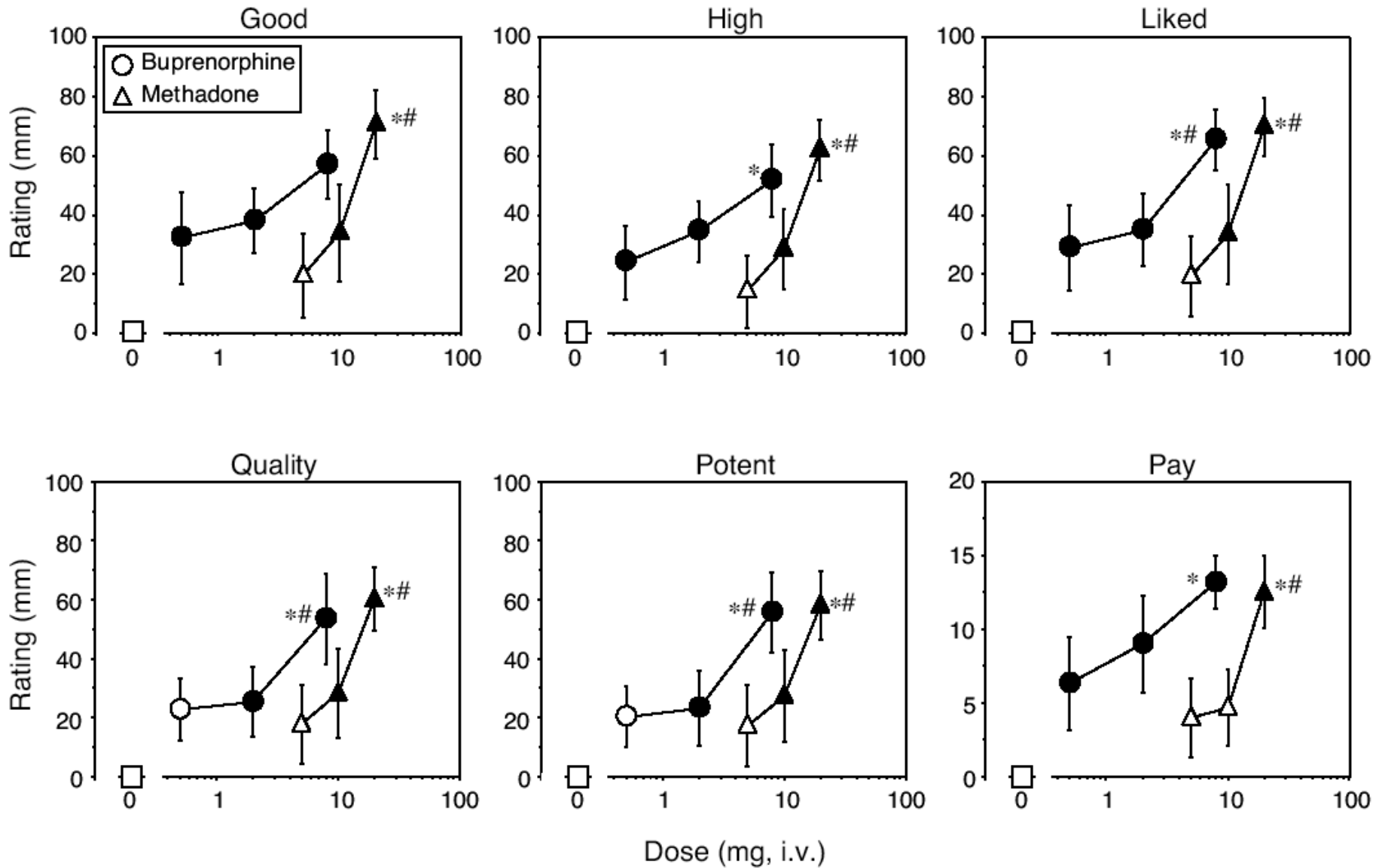
But it also has abuse liability and, in some countries, has largely replaced heroin as the opioid of choice among abusers

BACKGROUND

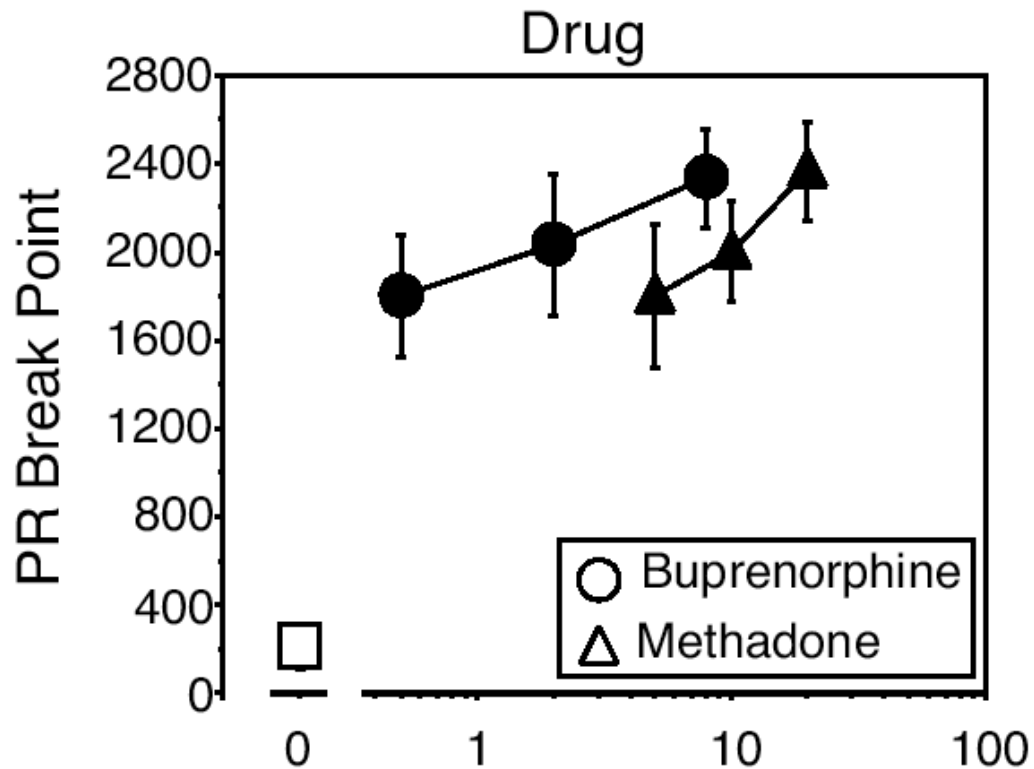
Previous studies in our laboratory have shown that:

- 1) In non-dependent heroin abusers, IV buprenorphine and buprenorphine/naloxone produced robust reinforcing effects (Comer et al., 2002; Comer & Collins, 2002; Comer et al., 2005)
 - 2) In contrast, in morphine-maintained heroin abusers, IV buprenorphine had no reinforcing effects (Comer et al., 2008)
- ❖ The reinforcing effects of IV buprenorphine and buprenorphine/naloxone in buprenorphine-maintained individuals have not been studied

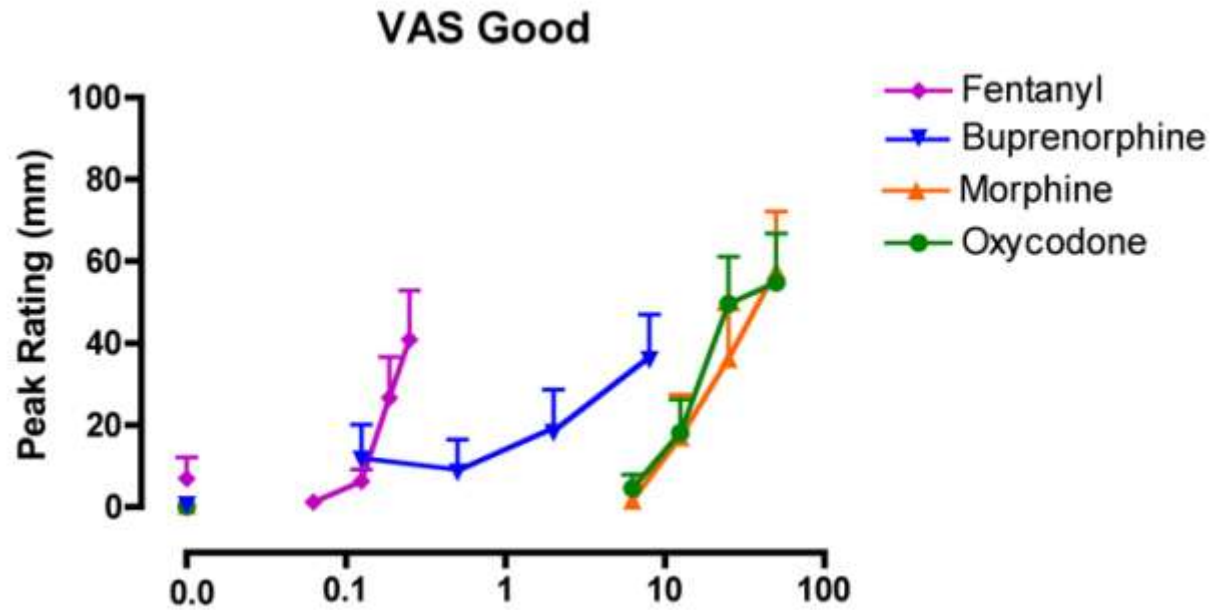
Non-opioid dependent



Non-opioid dependent

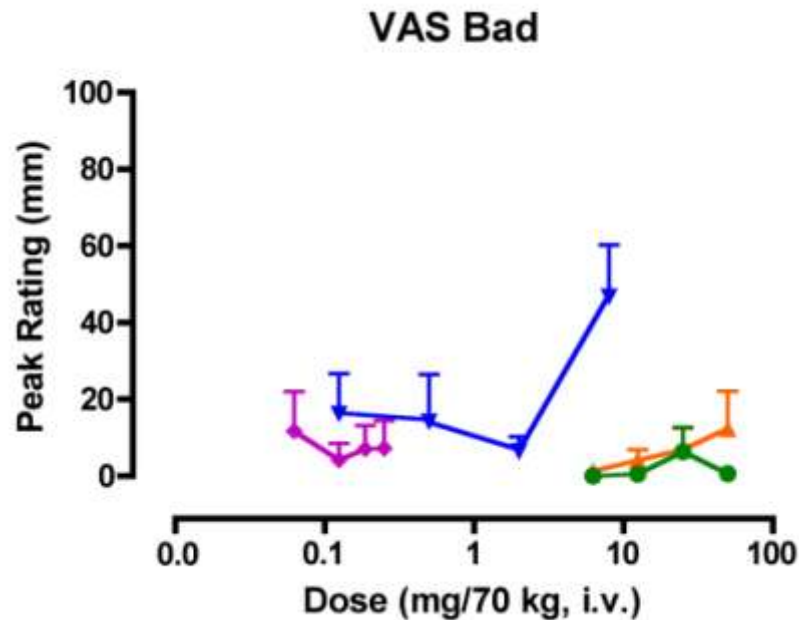
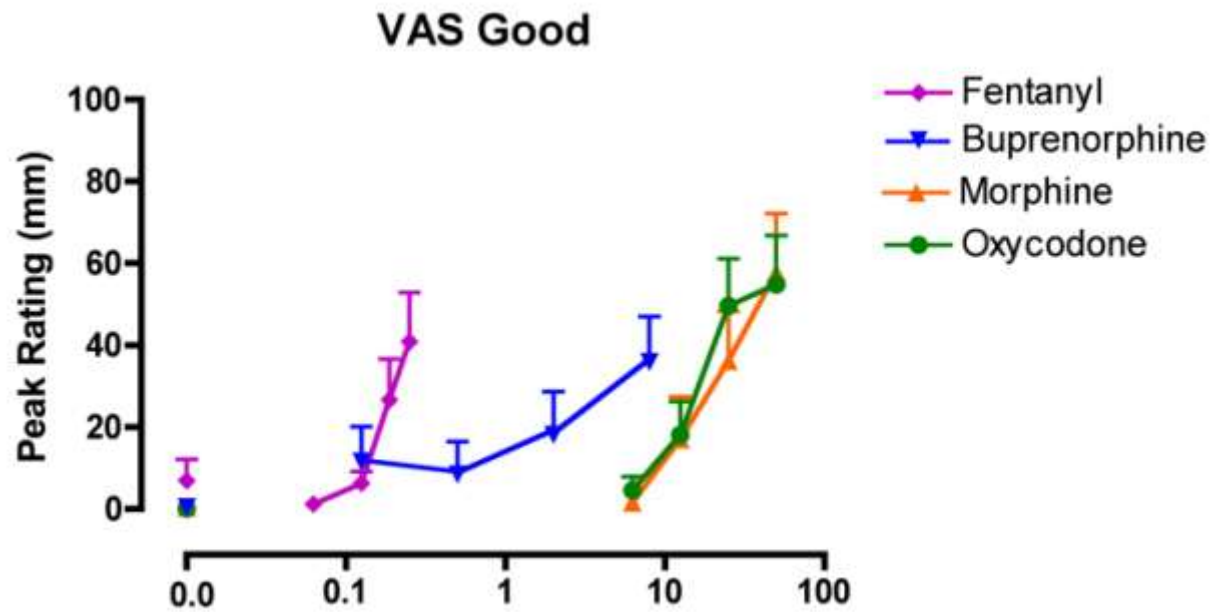


Morphine dependent



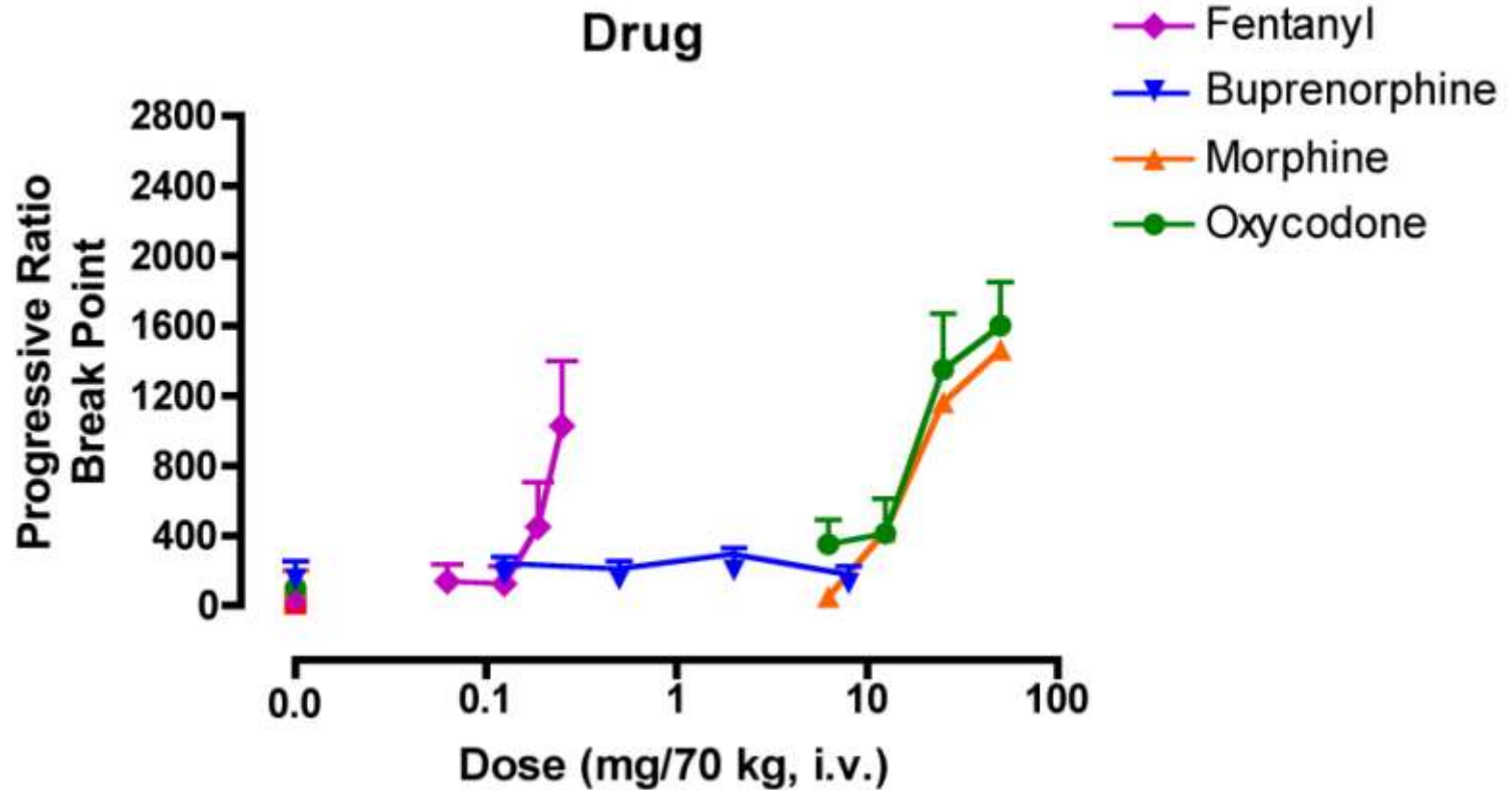
*Comer et al.,
Neuropsychopharm,
2008*

Morphine dependent



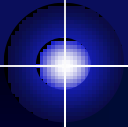
*Comer et al.,
Neuropsychopharm,
2008*

Morphine dependent



Comer et al., Neuropsychopharm, 2008

Buprenorphine dependent?



Primary Aim

Simulate French buprenorphine injectors by comparing the reinforcing effects of IV buprenorphine (BPN) and buprenorphine/naloxone (BNX) in injection drug users maintained on different doses of sublingual buprenorphine (2, 8, 24 mg)

Secondary Aims

Compare the subjective, physiologic, and performance effects of IV BPN and IV BNX

Experimental Design

Design: Randomized, double-blind, cross-over study

Subjects: Heroin-dependent and not seeking treatment

Setting: Lived in the hospital during the 8-week study

Subjects: 12 completers

Maintenance drug: SL Buprenorphine (2, 8, 24 mg)

Intravenous (IV) test doses:

- Buprenorphine/Naloxone (BNX: low, high)

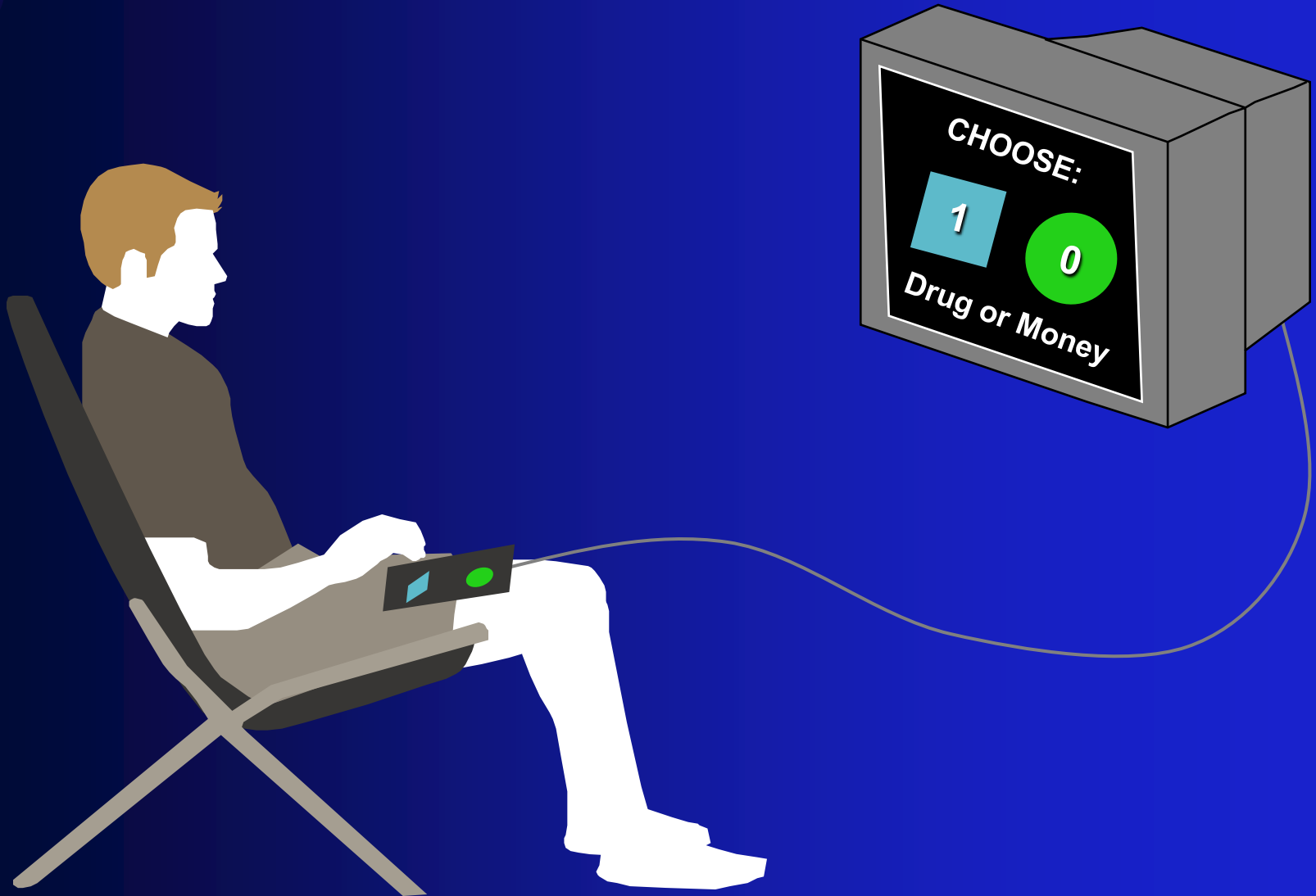
- Buprenorphine (BPN: low, high)

- Placebo (Pbo)

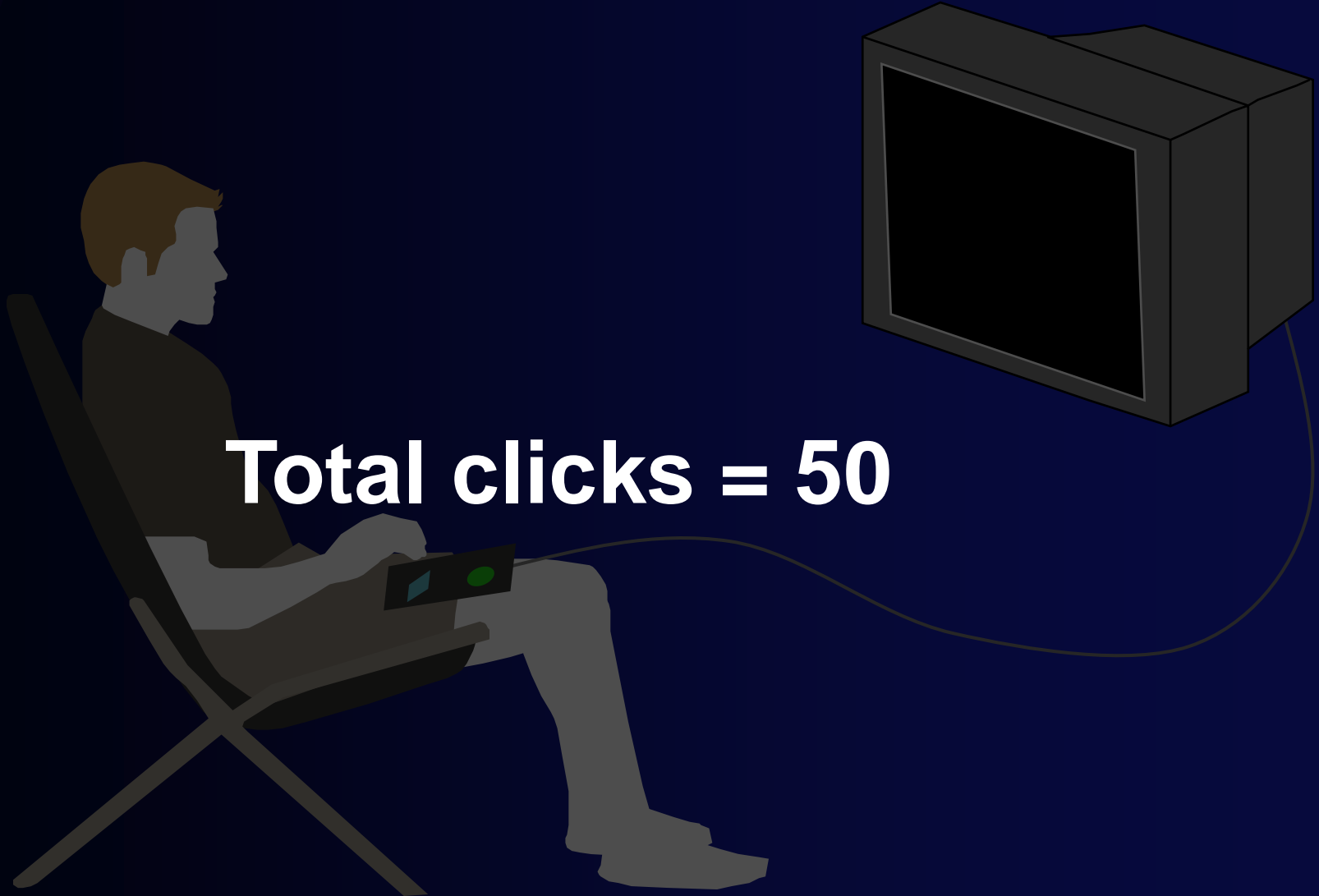
- Naloxone (Nx)

- Heroin (25 mg)

Drug vs Money Choice Procedure

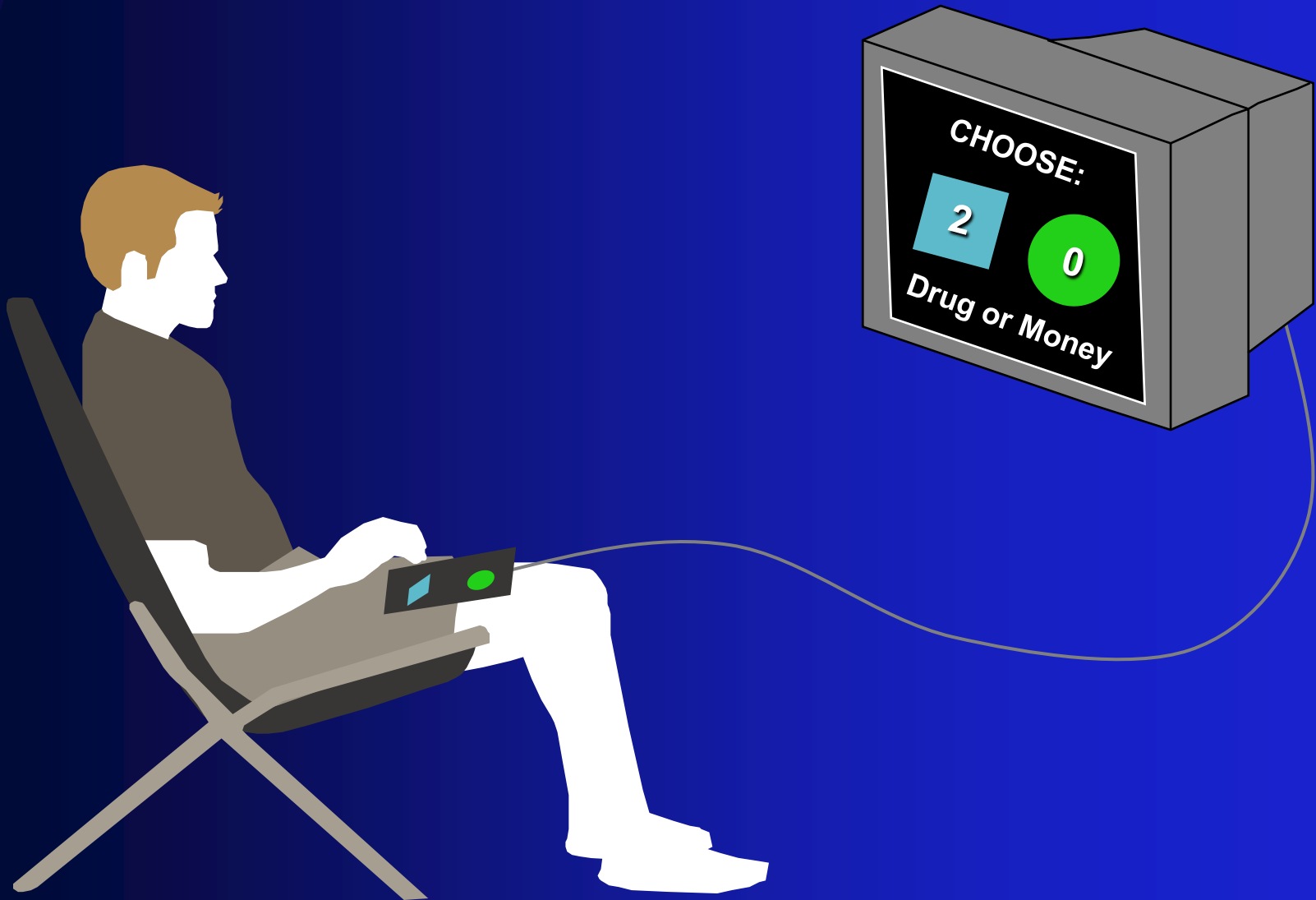


Drug vs Money Choice Procedure

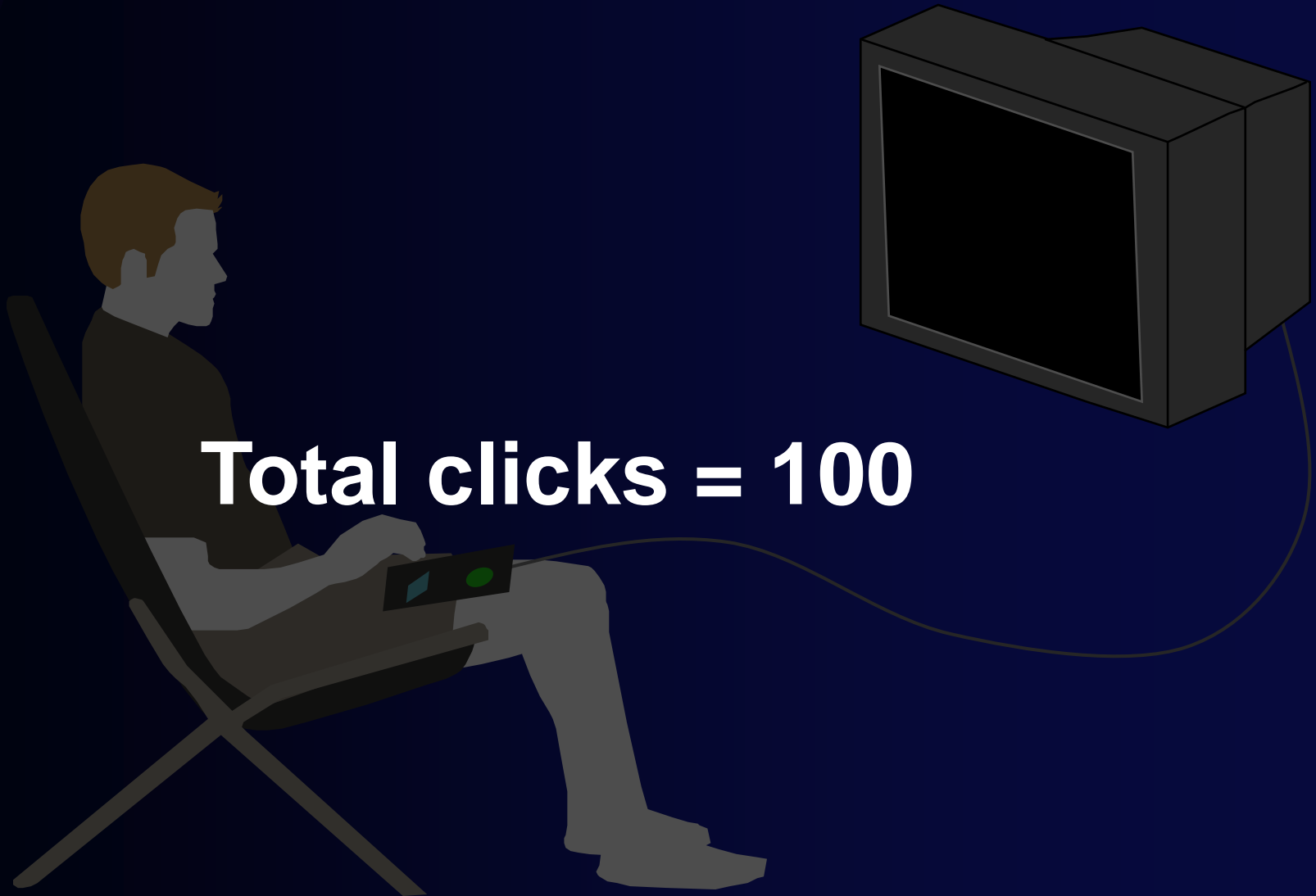


Total clicks = 50

Drug vs Money Choice Procedure

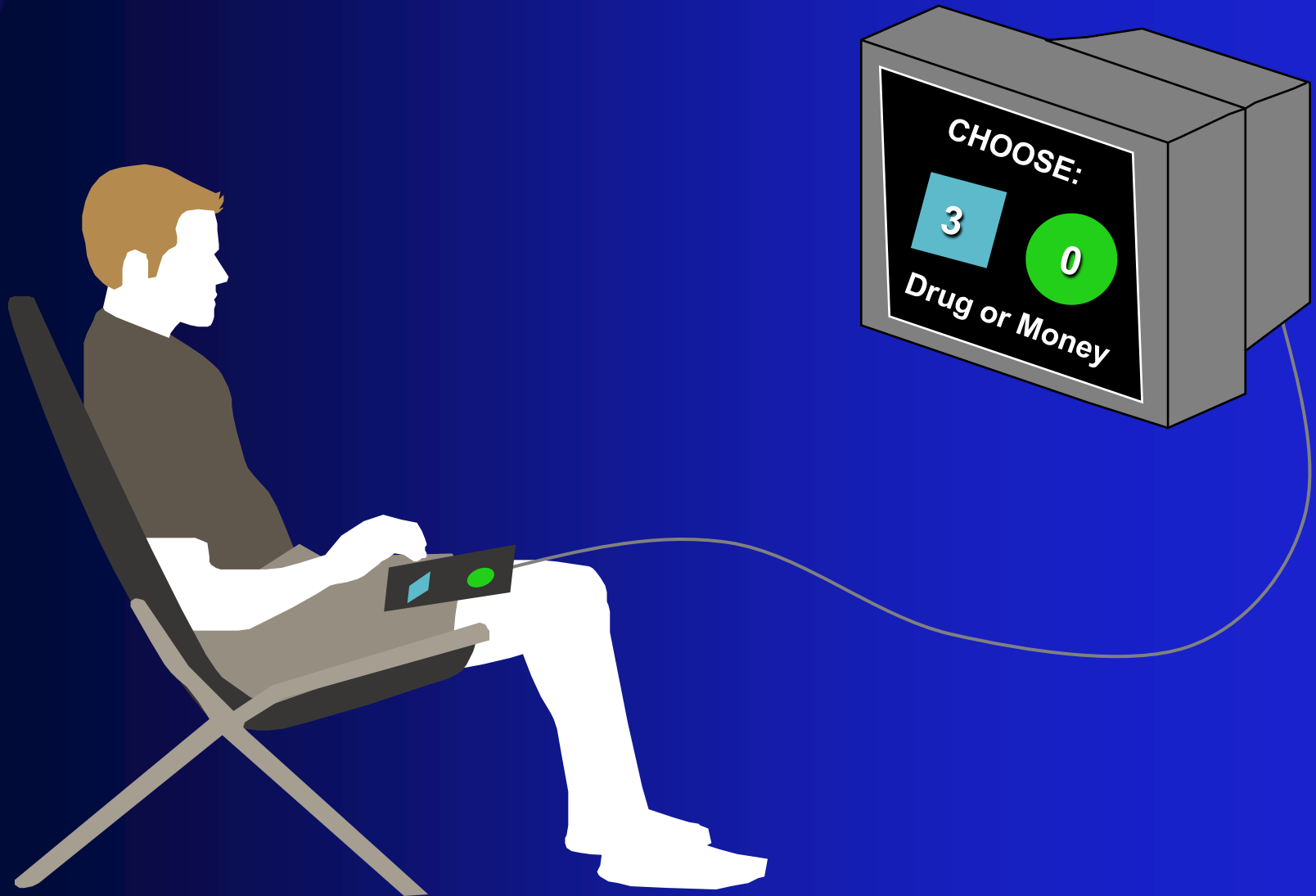


Drug vs Money Choice Procedure



Total clicks = 100

Drug vs Money Choice Procedure

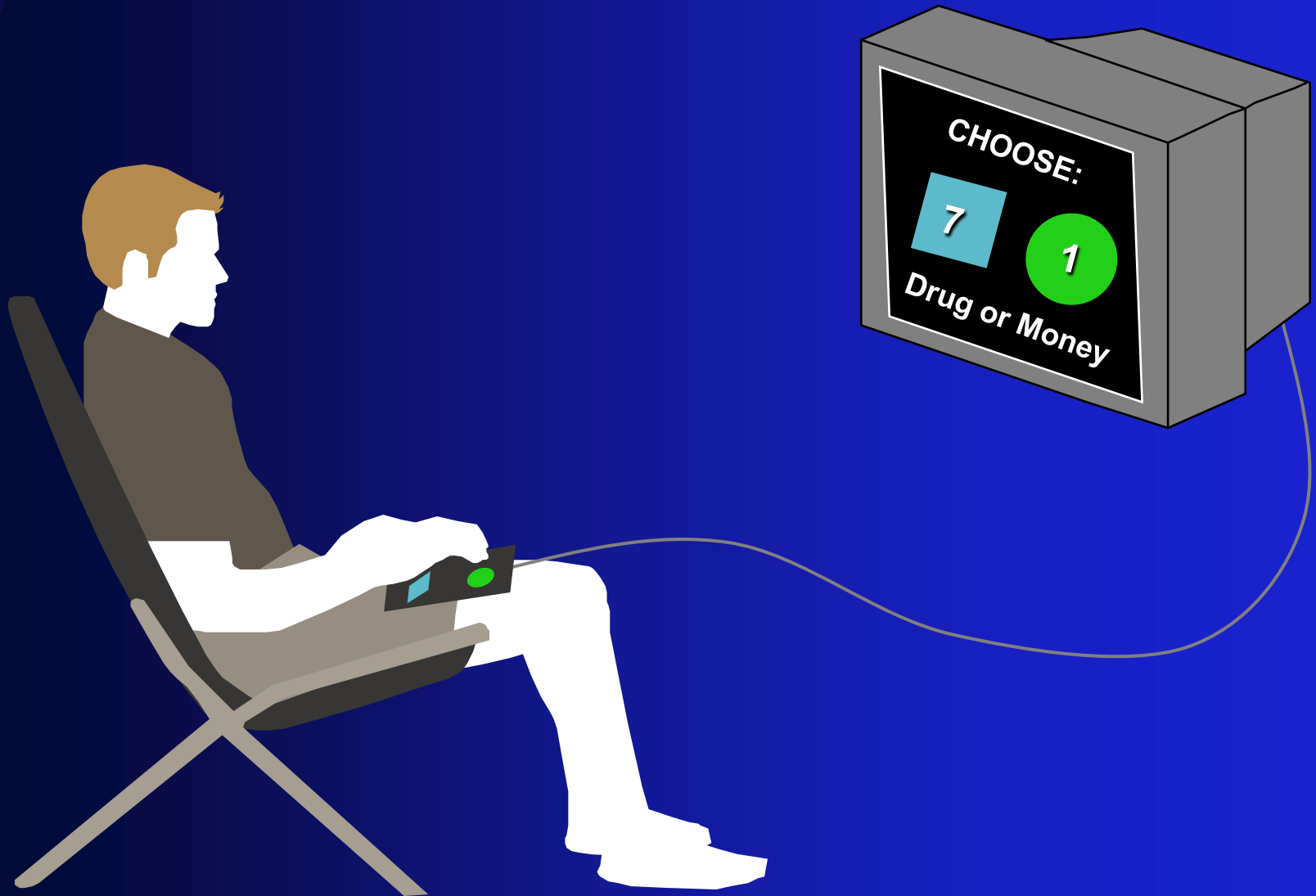


Drug vs Money Choice Procedure

After 7 trials
(Total clicks on 7th trial = 1600)



Drug vs Money Choice Procedure

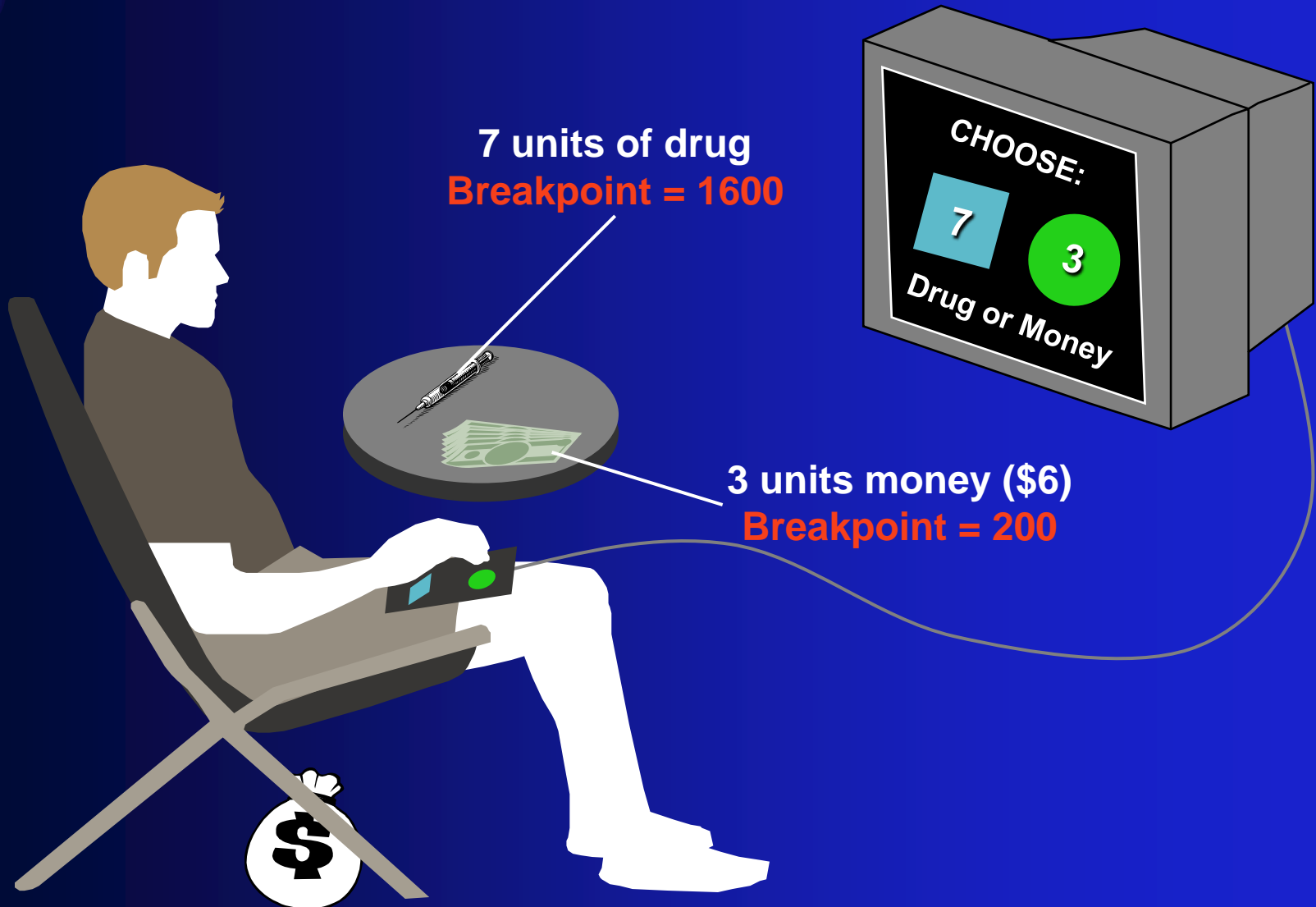


Drug vs Money Choice Procedure



Total clicks = 50


Drug vs Money Choice Procedure



Drug vs Money Choice Procedure



Experimental Design

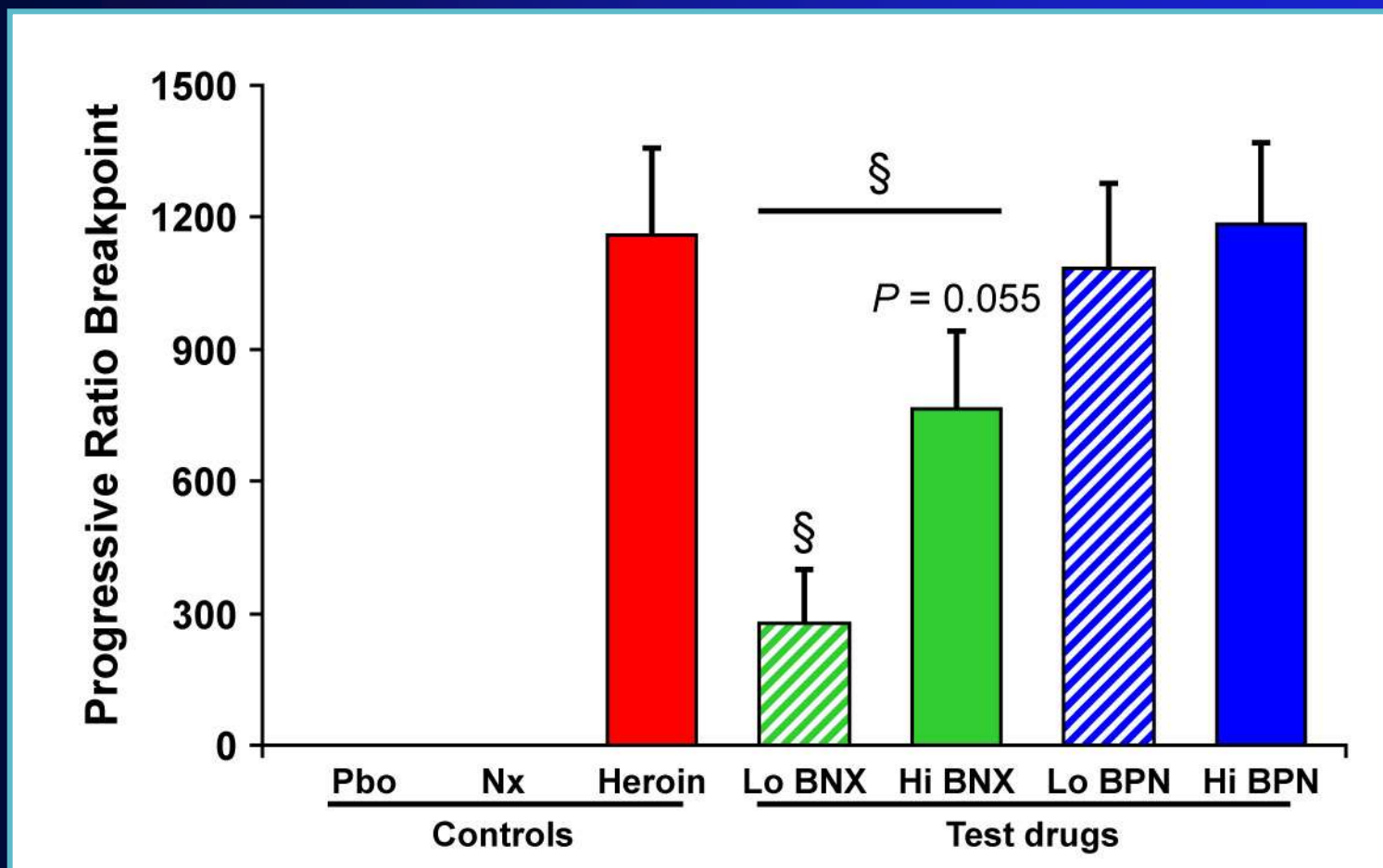
Study Phase	SL Buprenorphine Maintenance	IV Test Doses
Qualification	2 mg	Stabilization (5-6 days) Pbo, 2, 2, 4, 8, 16 mg BPN (6 days)
		 Criterion: must self-administer 4, 8 or 16 mg BPN more than they self-administer Pbo
Test	2 mg	Stabilization (5-6 days) Pbo, Nx, Heroin, Lo BNX, Hi BNX, Lo BPN, Hi BPN
Test	8 mg	Stabilization (5-6 days) Pbo, Nx, Heroin, Lo BNX, Hi BNX, Lo BPN, Hi BPN
Test	24 mg	Stabilization (5-6 days) Pbo, Nx, Heroin, Lo BNX, Hi BNX, Lo BPN, Hi BPN

Participant Demographics

Sex	8M, 4F
Ethnicity	7 Caucasian 3 Hispanic 2 African Am
Age (yrs)	36.2
Heroin use (yrs)	11.3
Spent/day on heroin (\$)	67.03

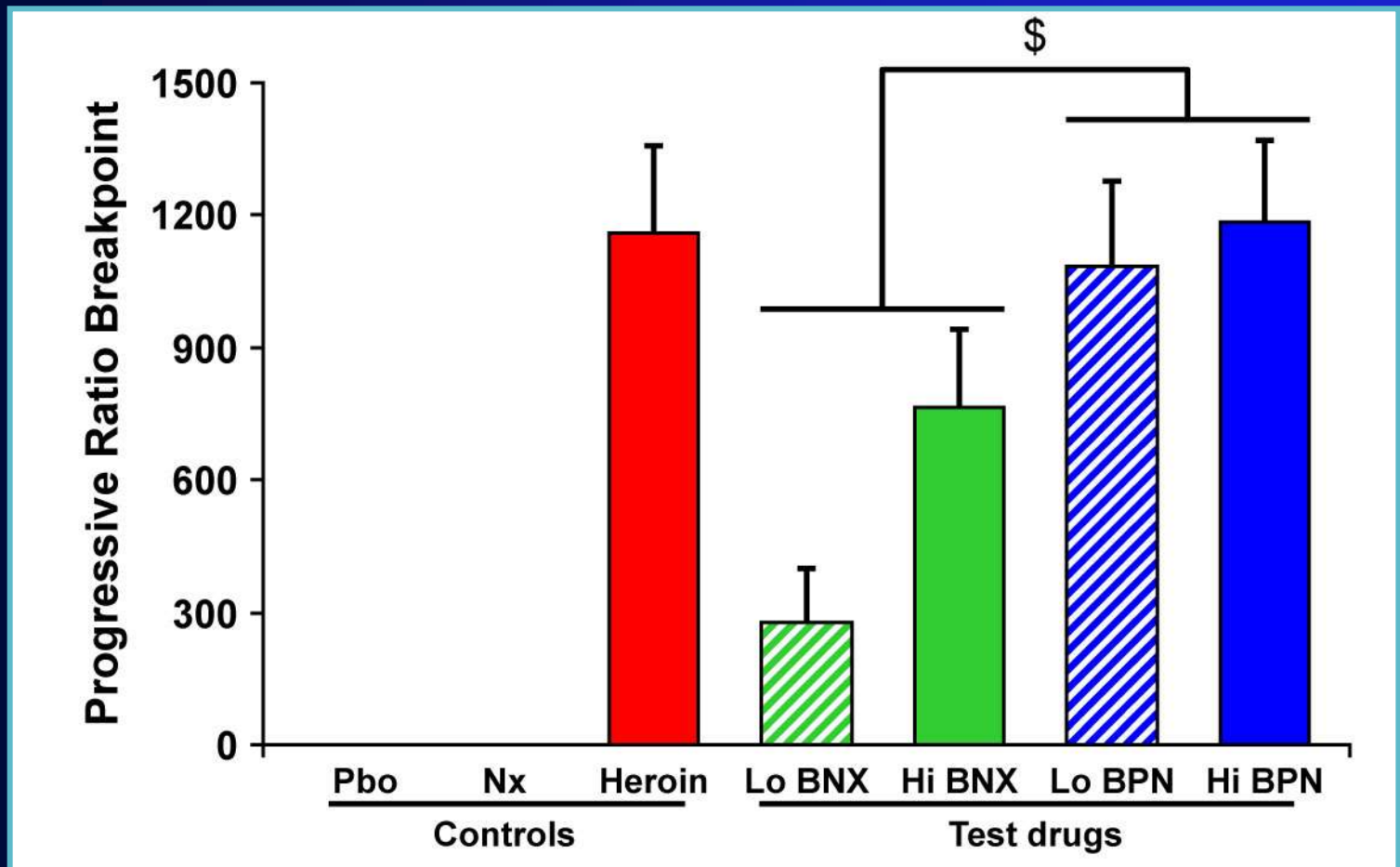
Primary End Point: Participants Self-Administered Low- and High-Dose BNX Less Frequently Than Heroin

§ Significant difference from heroin
($P = 0.0001$)



Primary End Point: Participants Self-Administered All Doses of BNX Less Frequently Than All Doses of BPN

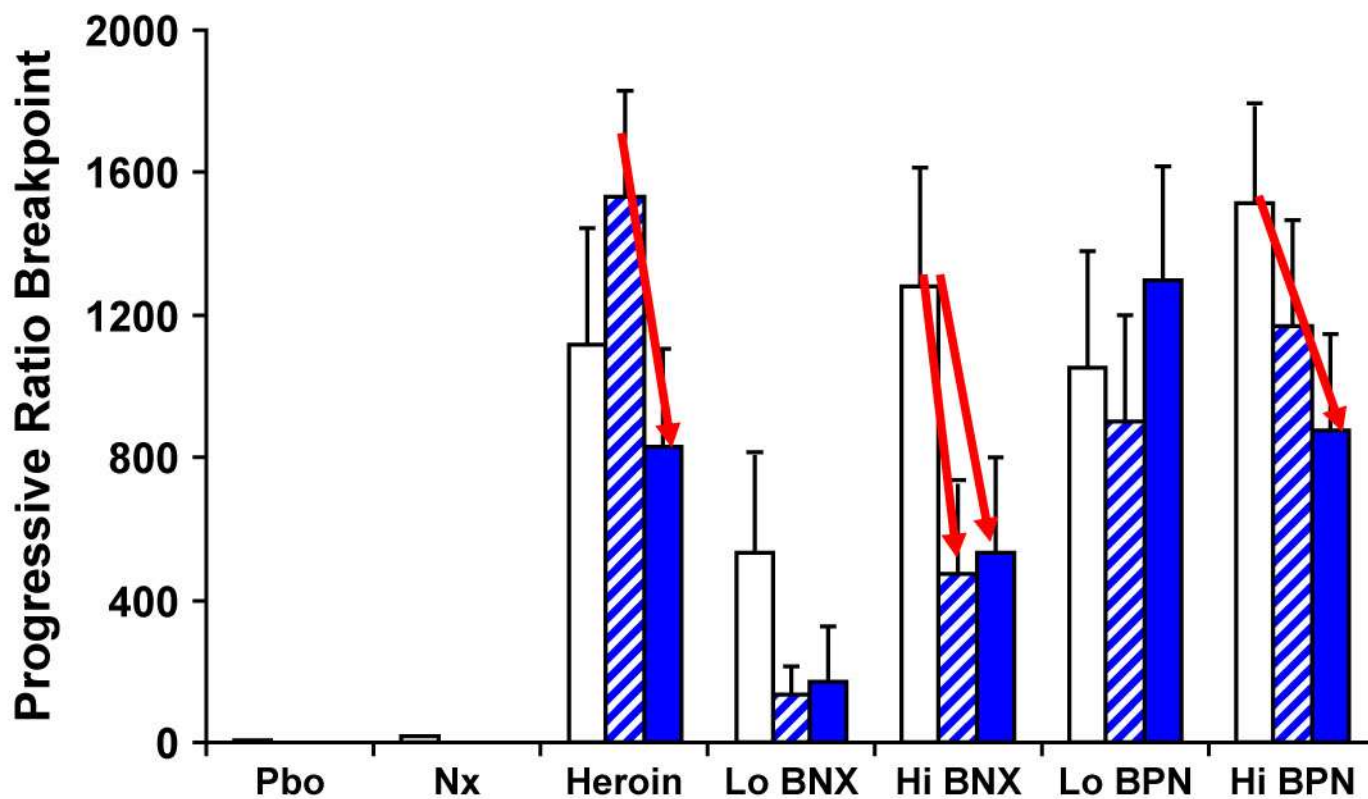
\$ Significant difference between BNX and BPN
($P = 0.0001$)



Participants Were More Likely to Self-Administer Drug When Maintained on 2 mg SL BPN Compared to Higher Doses of SL BPN

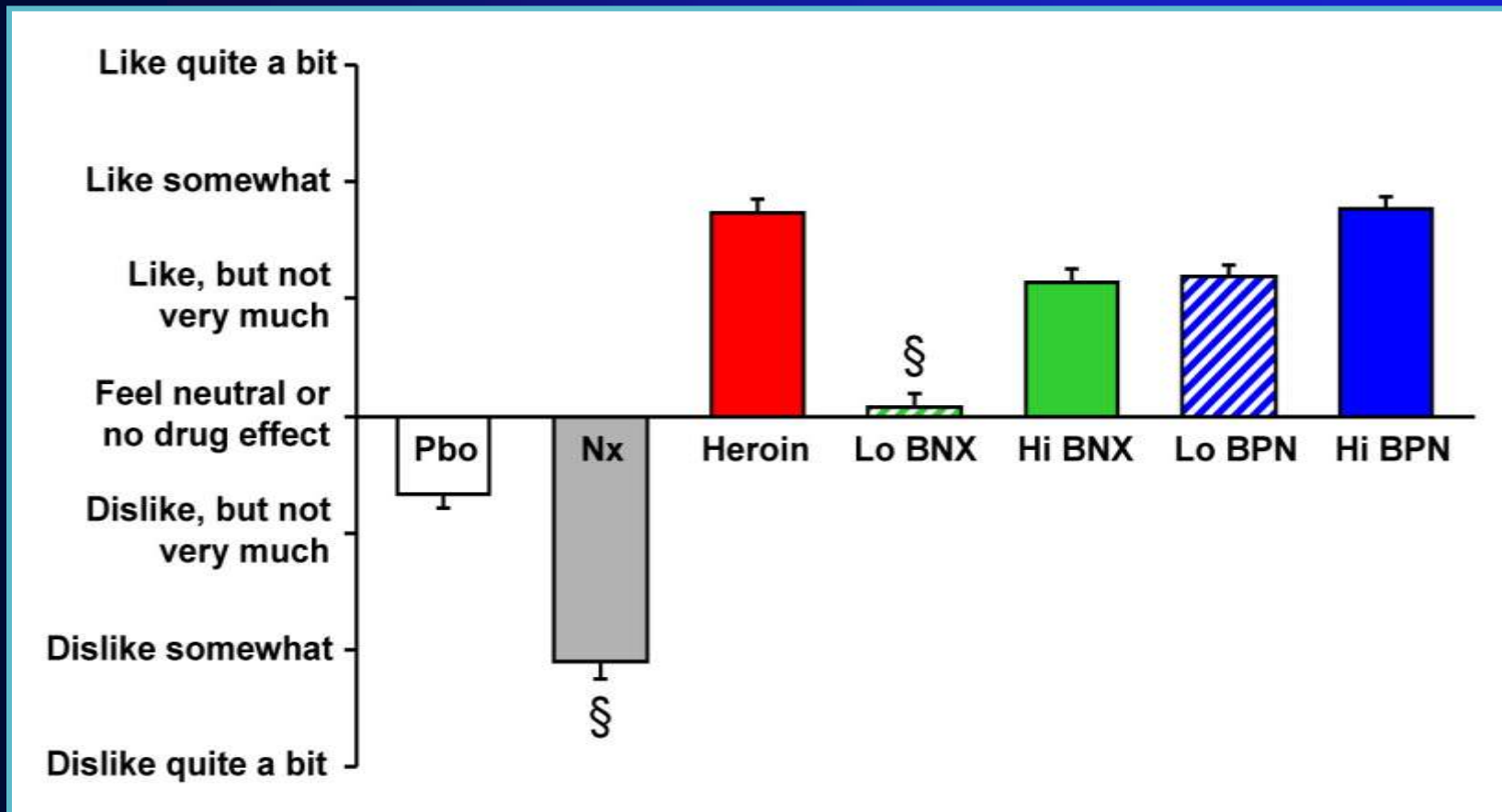
■ 2 mg
▨ 8 mg
■ 24 mg

→ Significant difference



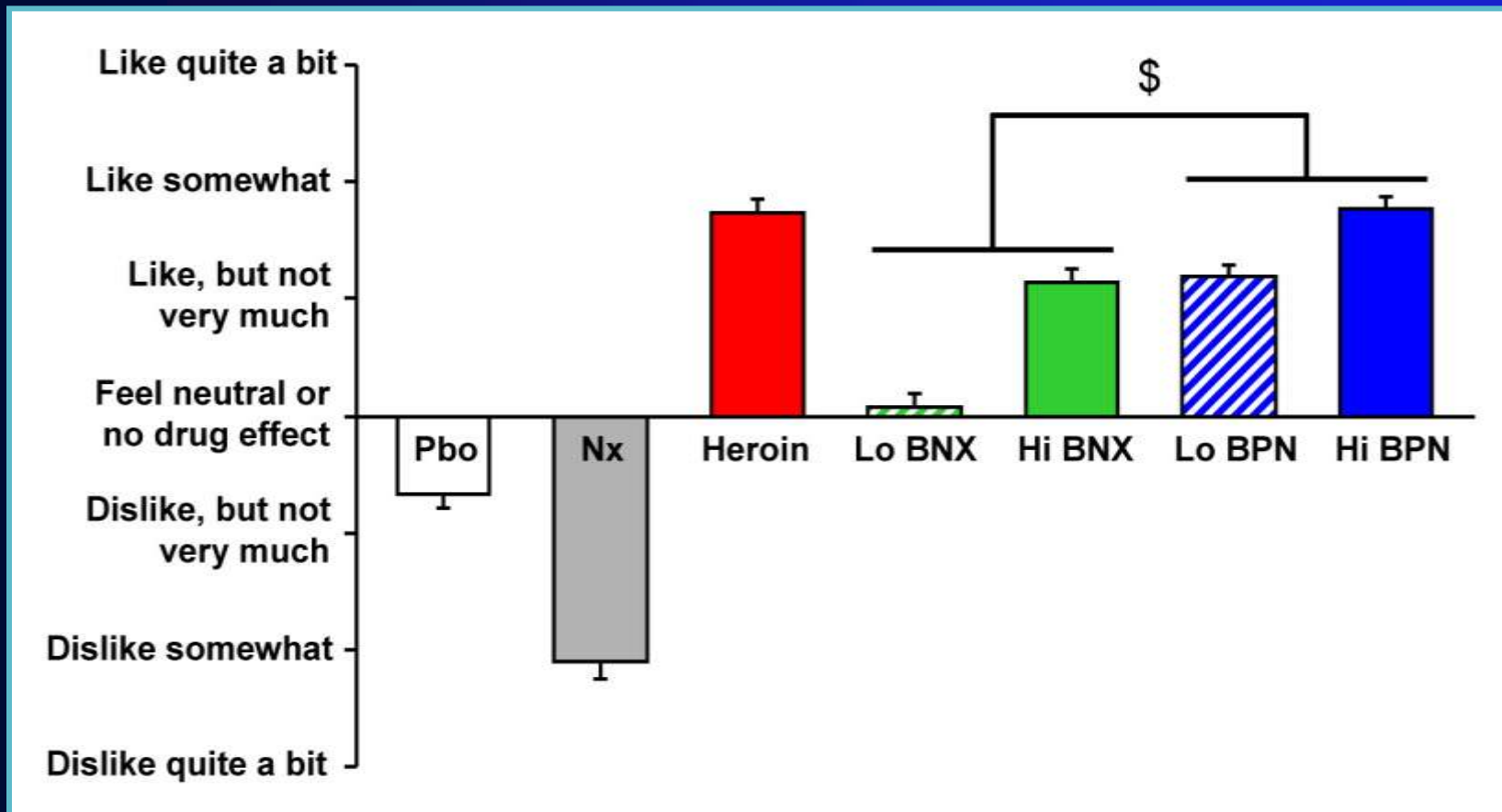
Compared With Heroin, Participants Reported Significantly Less “Drug Liking” for Naloxone and Low-Dose BNX

§ Significant difference from heroin
($P < 0.005$)



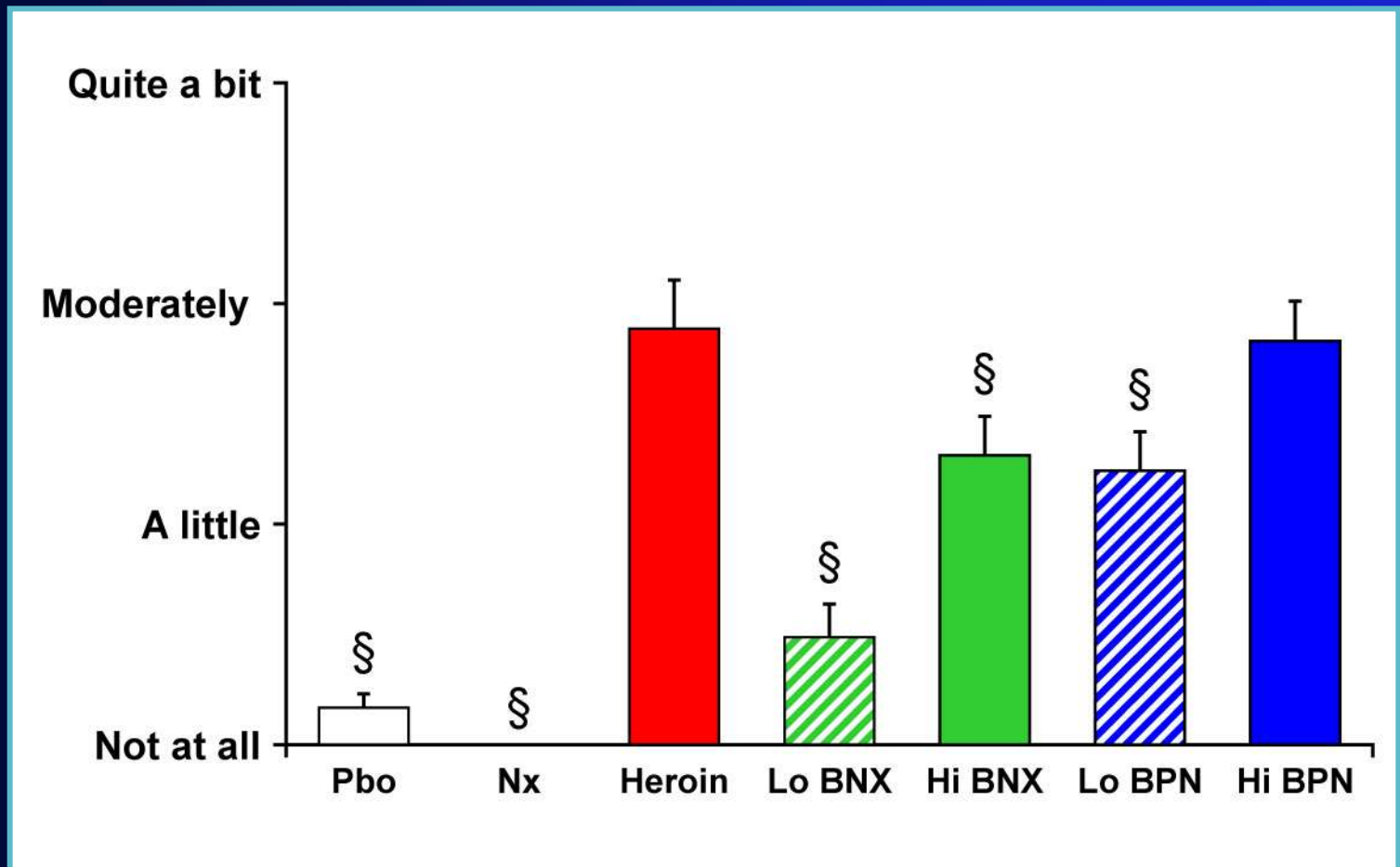
Participants Reported Liking Low- and High-Dose BNX Significantly Less Than BPN

\$ Significant difference between BNX and BPN
($P < 0.02$)



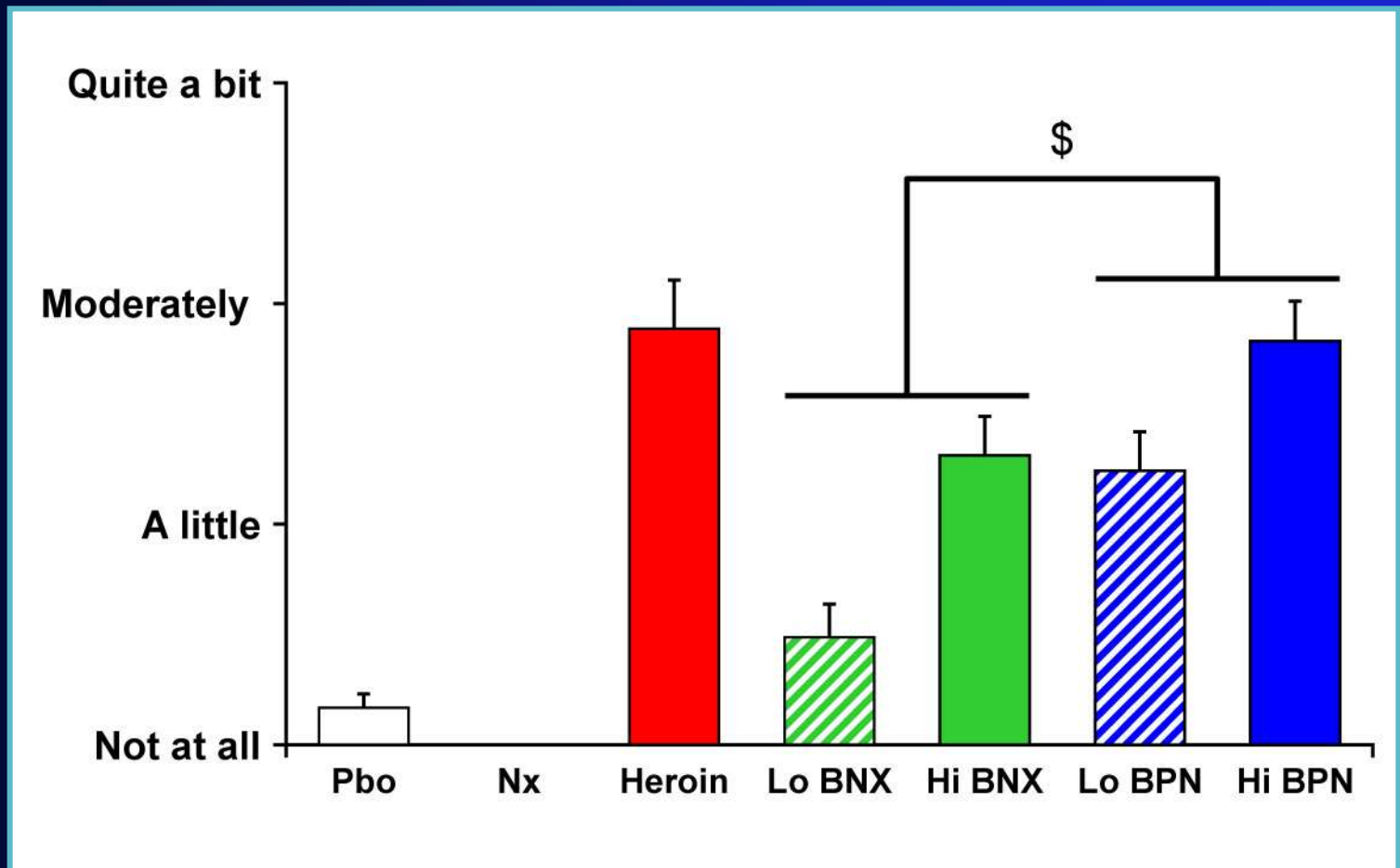
Compared With Heroin, All Participants Reported Significantly Less “Willingness to Take Drug Again” for All Drugs Except High-Dose BPN

§ Significant difference from heroin
($P < 0.005$)



Compared With BPN, Participants Reported Less “Willingness to Take Drug Again” for BNX

§ Significant difference between BNX and BPN
($P = 0.0001$)



Conclusions

Although IV BNX still does have abuse liability, it is less than IV BPN alone or heroin

Compared with BPN alone or heroin, participants:

- Were less likely to self-administer BNX
- Experienced less positive subjective effects with BNX
- Reported that they would pay less money for BNX

In addition:

- The abuse liability of BPN was similar to that of heroin
- Higher BPN maintenance doses were more effective than lower doses in reducing IV injection

Summary

These data support the notion that the combination product BNX has a lower abuse liability compared with BPN and heroin in BPN-dependent injectors

BNX is a good option for first-line treatment of opioid dependence because it is

- Safe and effective when taken sublingually¹
- Less likely to be abused by patients taking buprenorphine, and, therefore, a better option for take-home therapy

ACKNOWLEDGEMENTS

- Support from the Schering-Plough corporation for this research project is gratefully acknowledged

ACKNOWLEDGEMENTS

- Maria Sullivan, MD, PhD
- Jeanne Manubay, MD
- Suzanne Vosburg, PhD
- Ziva Cooper, PhD
- Janet Murray, RN
- Ronnie Shapiro, RN
- Phillip Saccone, BS
- Joseph Lazar, BS
- William Kowalczyk, BS
- Susanna Stephens, BS
- Benjamin Bryan, MD
- Soteri Polydorou, MD
- Jennifer Hanner, MD
- Stanislav Vorel, MD