Current Status of Human Abuse Liability Studies: Methods, Outcomes, and Predictive Validity

Sandra D. Comer, Ph.D.

College of Physicians & Surgeons of Columbia University
Department of Psychiatry
Division on Substance Abuse

New York State Psychiatric Institute

Goals

- Describe the methods that are used to evaluate the abuse liability of drugs
- Compare outcomes from clinical abuse liability trials with clinical treatment trials and with epidemiological data

Methodology

The “Gold Standard”

ELSEVIER

Drug and Alcohol Dependence 70 (2003) S41–S54

DRUG and ALCOHOL DEPENDENCE

www.elsevier.com/locate/drugalcdep

Principles of initial experimental drug abuse liability assessment in humans☆

Roland R. Griffiths [a,b,*], George E. Bigelow [a], Nancy A. Ator [a]

[a] *Department of Psychiatry and Behavioral Sciences, Johns Hopkins University School of Medicine, 5510 Nathan Shock Drive, Baltimore, MD 21224, USA*

[b] *Department of Neuroscience, Johns Hopkins University School of Medicine, Baltimore, MD, USA*

Typical Design Characteristics

- Complete crossover design in 10-14 subjects
- Single doses evaluated over time
- Intervals between test conditions: one day to several days

Setting

- Controlled clinical pharmacology laboratory
  - Inpatient to minimize other drug use and to provide stable day-to-day routines
  - Sometimes outpatient, but many drawbacks

Selection of Subject Population

- Usually subjects with histories of polydrug abuse
- Population must be one in which the positive control comparison drug tests unequivocally positive

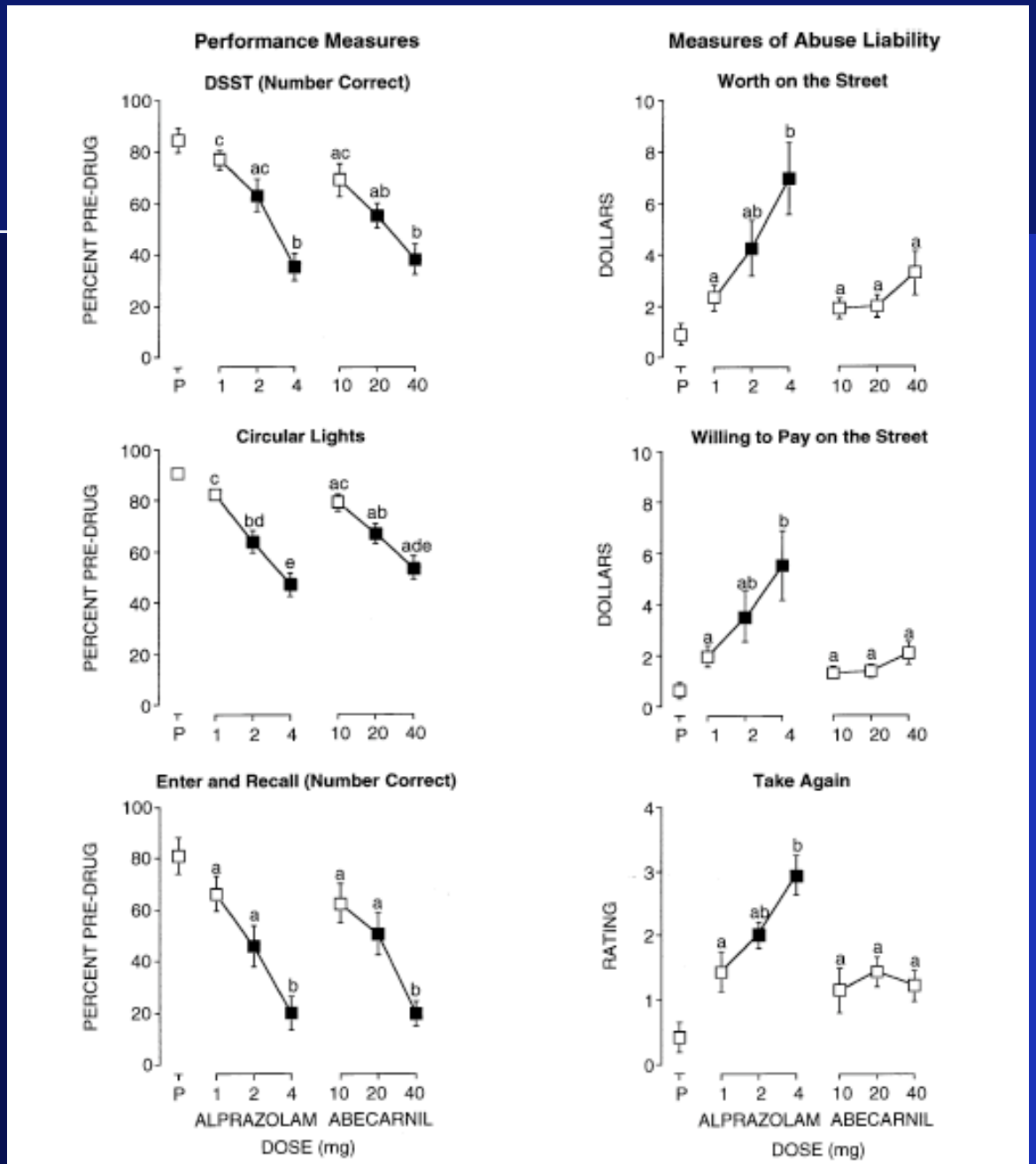
- Subjects are paid for study participation and are not seeking treatment for their drug use

Drug Administration

- Double blind, placebo controlled
- Positive control comparison drug(s)
  - Same pharmacological class and indication
  - Sometimes negative control from same class that is behaviorally active but not abused
- Appropriate dose range
  - Positive control: Orderly dose-effects to establish sensitivity and validity of the trial
  - Novel compound: Supratherapeutic doses

Outcome Measures

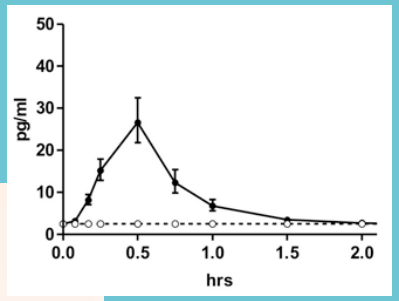
- Measures assessed repeatedly to characterize onset, peak, and offset of drug effects
- Multiple measures used to reflect likelihood of abuse
  - e.g., liking, good effects, estimated monetary street value
- Behavioral performance, observer ratings, physiological measures


Performance Measures
DSST (Number Correct)
PERCENT PRE-DRUG
Circular Lights
Enter and Recall (Number Correct)
Measures of Abuse Liability
Worth on the Street
DOLLARS
Willing to Pay on the Street
Take Again
RATING
P 1 2 4 10 20 40
ALPRAZOLAM ABECARNIL
DOSE (mg)

Hospital setting

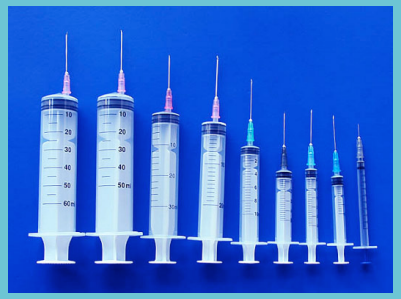
"I feel high"

Multiple measures



Timecourse

Single dose per session



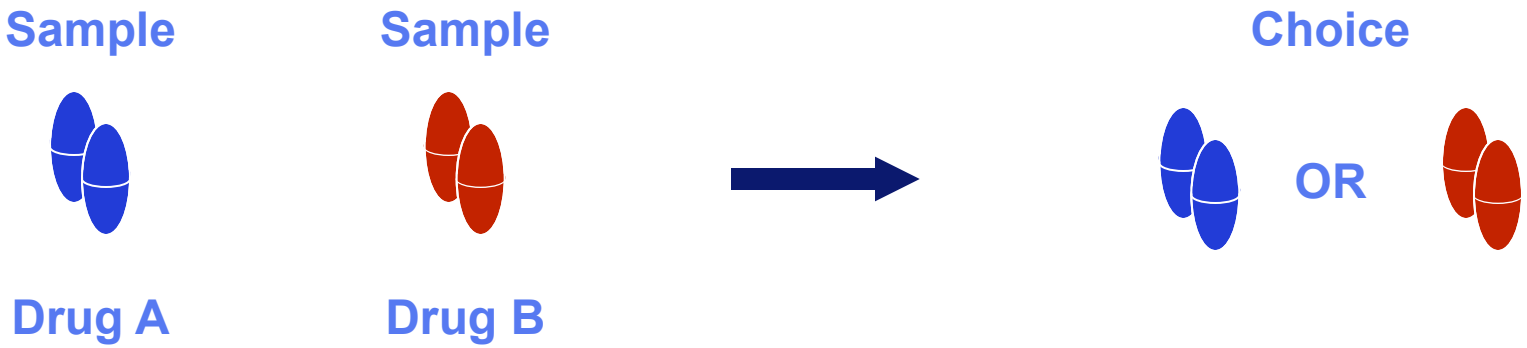
Multiple doses per study

Comparator drug

Additional Outcome Measures

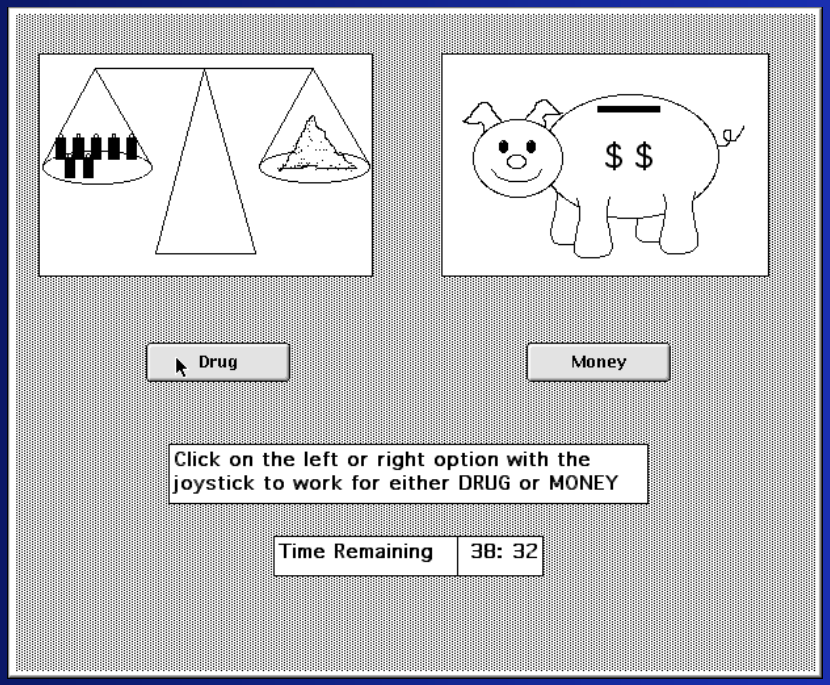
- Behavioral measures of drug taking behavior (the reinforcing effects of drugs)
  - Simple drug versus drug or drug versus money choice
  - Fixed ratio responding using PCA technology
  - Progressive ratio responding
  - Multiple choice procedure*

Drug versus Drug Choice



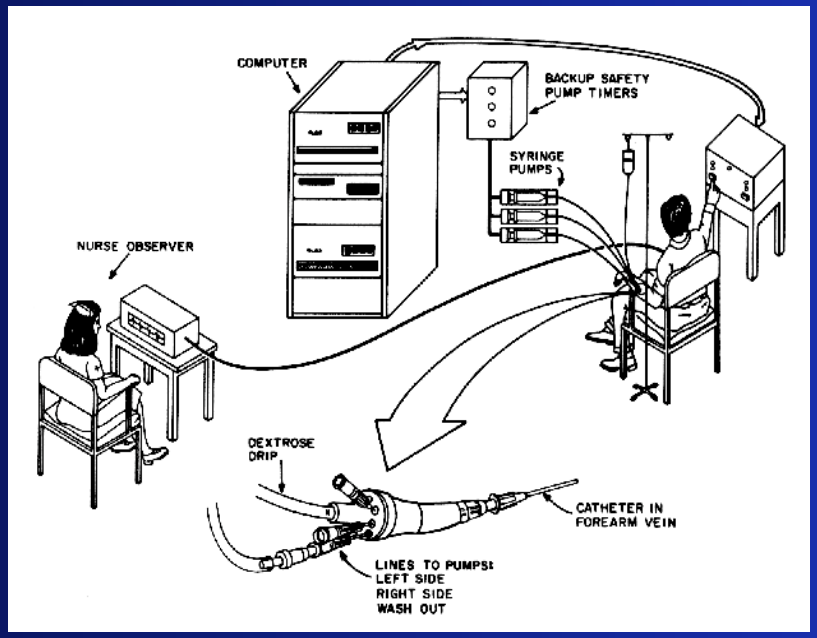
Objective: Measure the number of times drug is chosen over another drug or placebo

Drug versus Money Choice



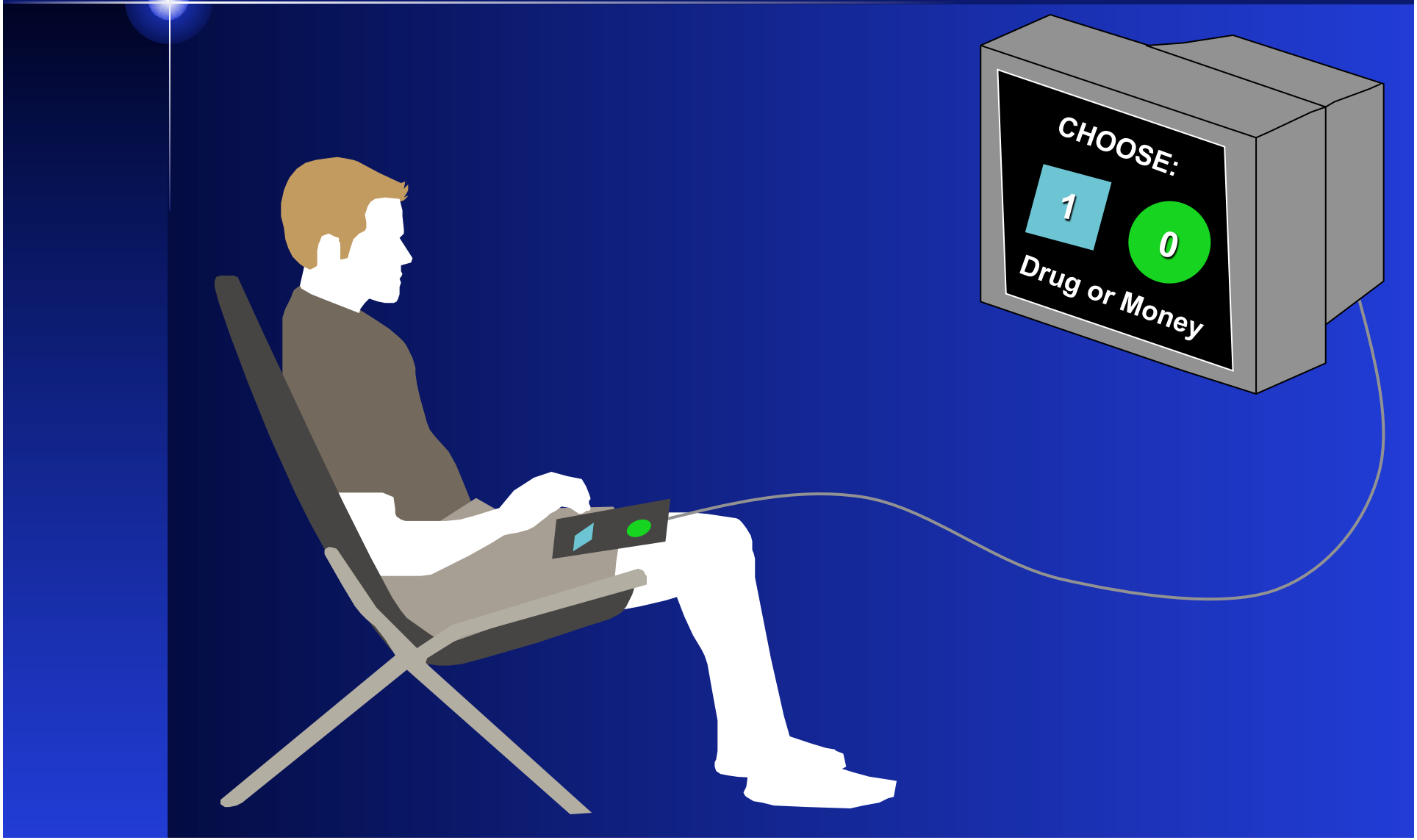
Objective: Measure the amount of responding elicited by the test drug and preference for drug over money

Patient-Controlled Analgesia



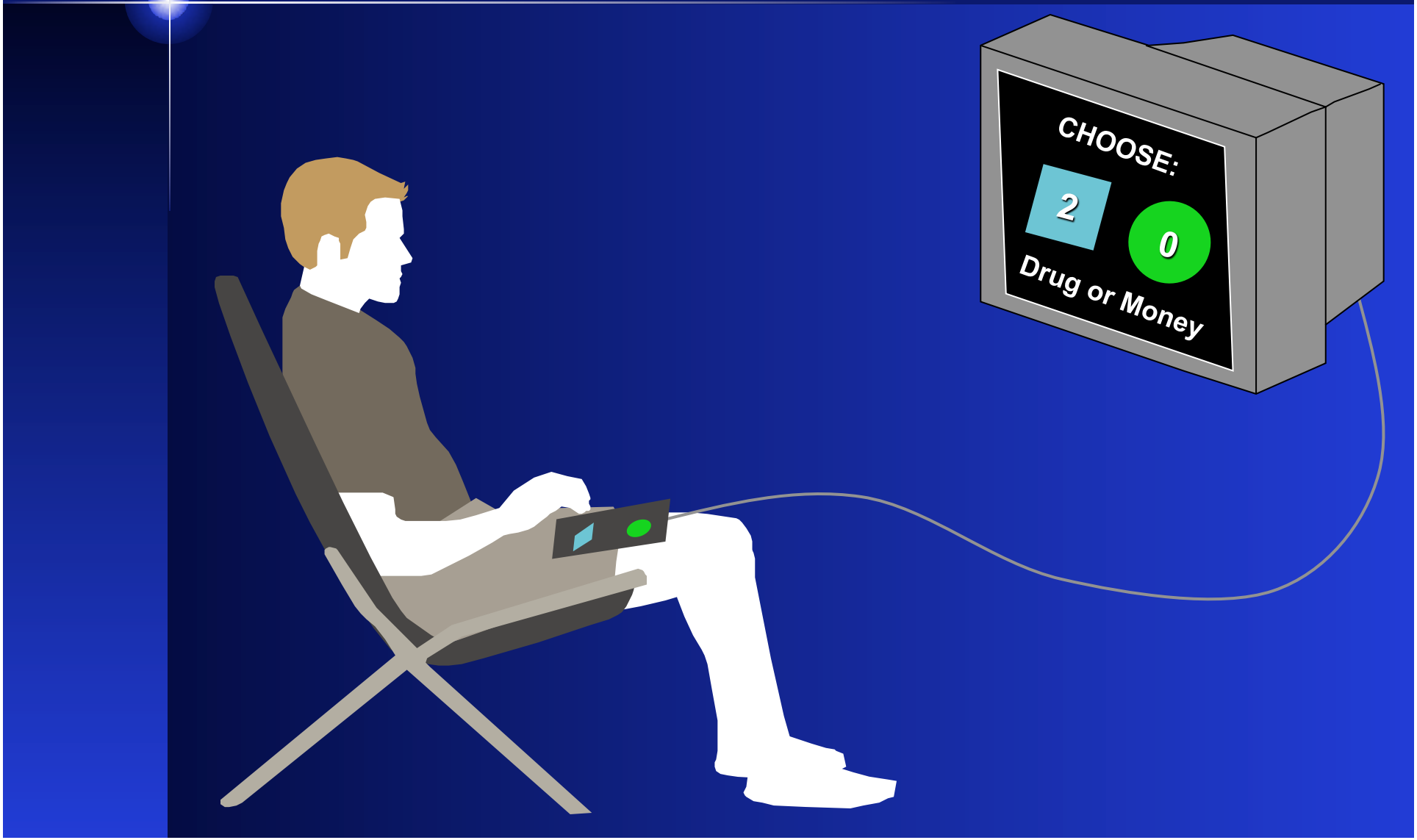
Objective: Measure the amount of responding elicited by the test drug

Drug vs Money Choice Procedure



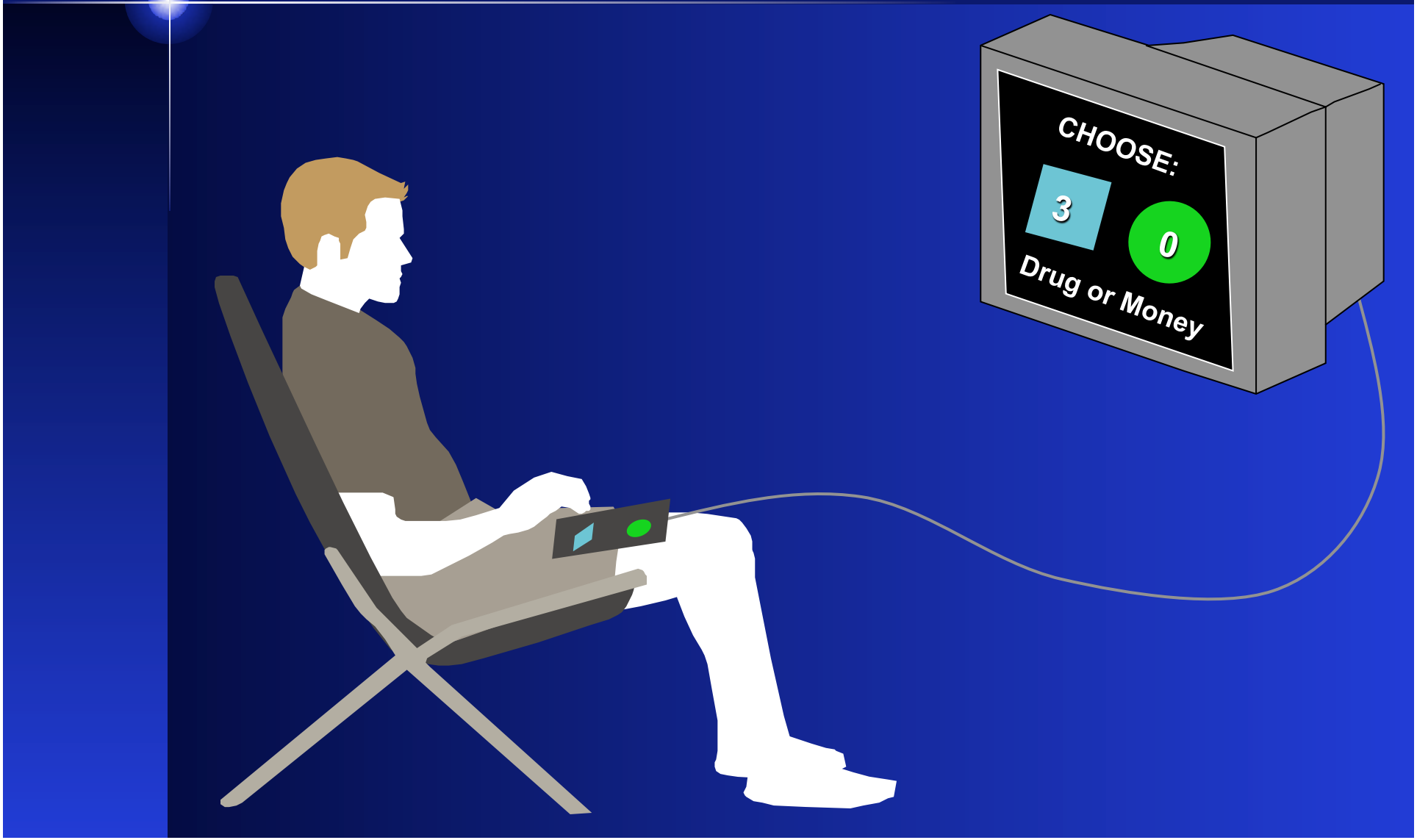
Drug vs Money Choice Procedure

Drug vs Money Choice Procedure

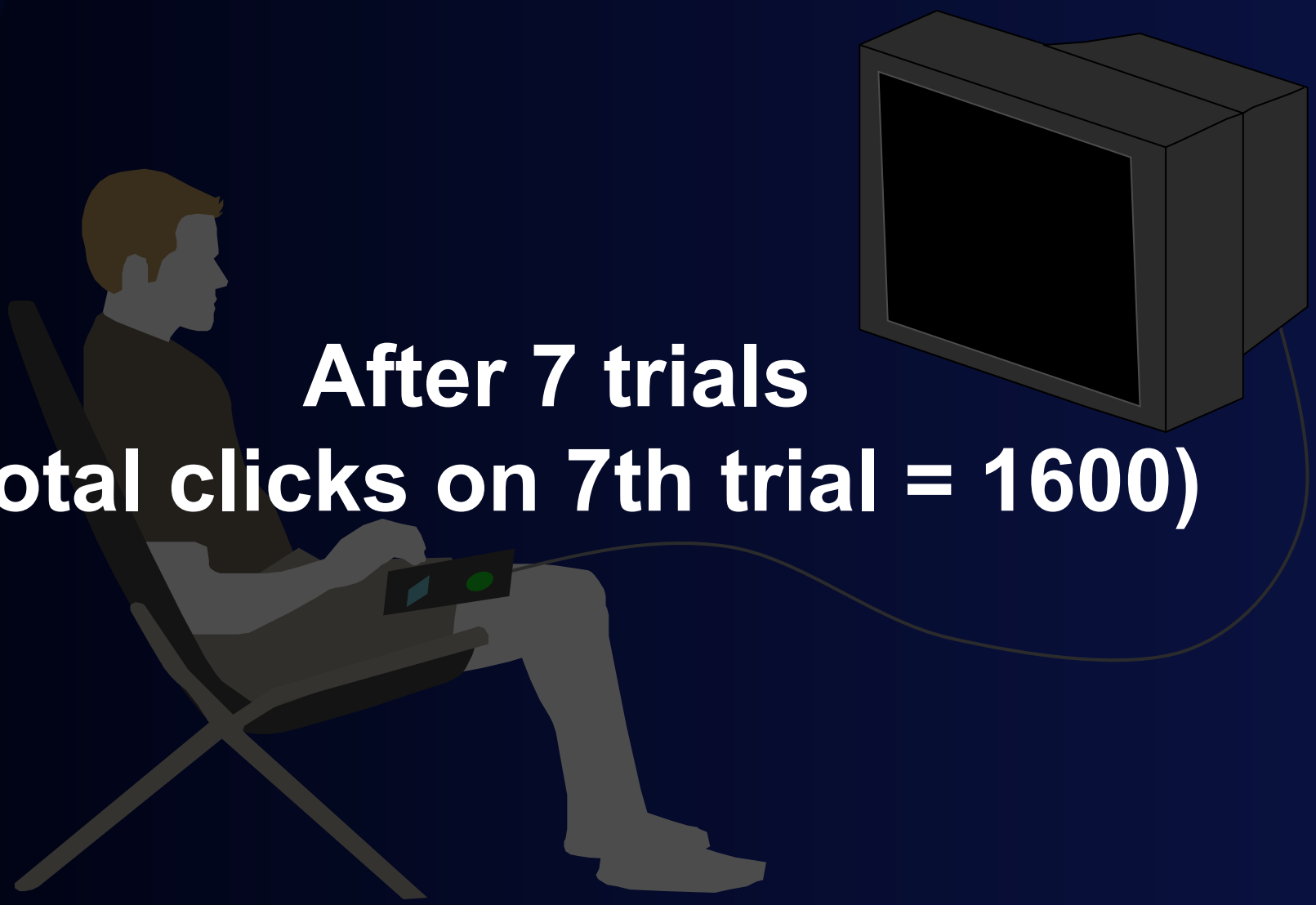


Drug vs Money Choice Procedure

Drug vs Money Choice Procedure

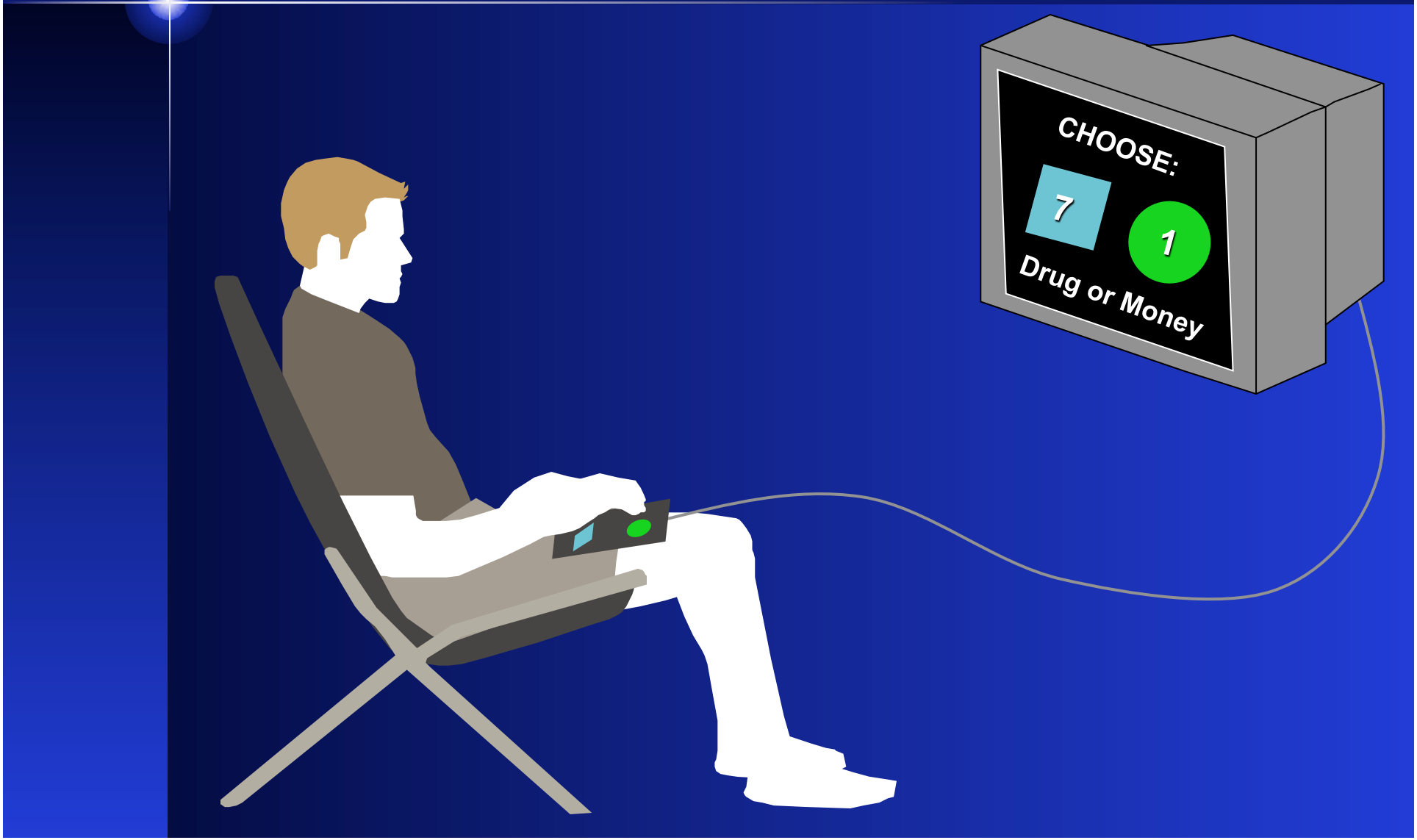


Drug vs Money Choice Procedure



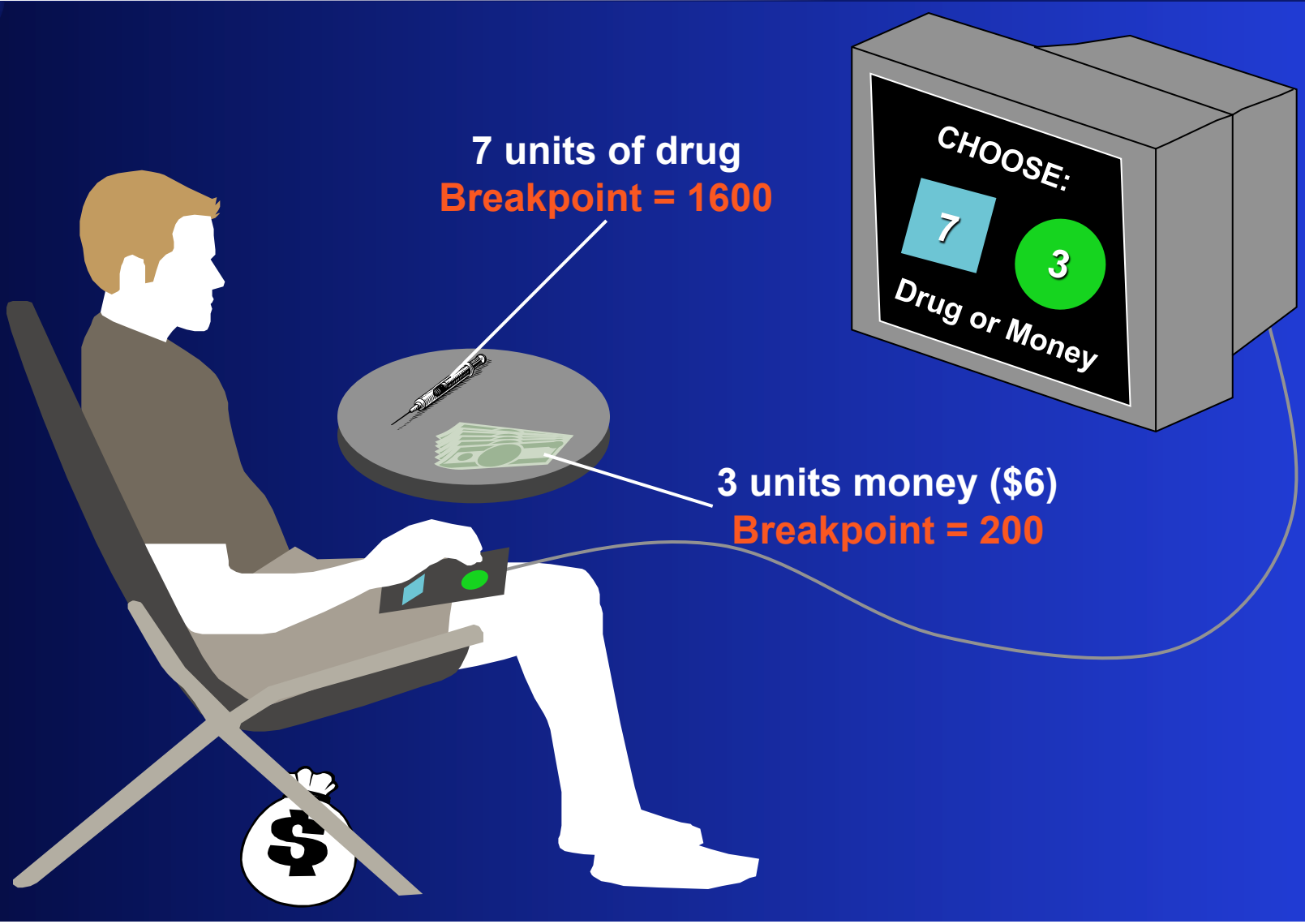
After 7 trials
(Total clicks on 7th trial = 1600)

Drug vs Money Choice Procedure



Drug vs Money Choice Procedure

Drug vs Money Choice Procedure



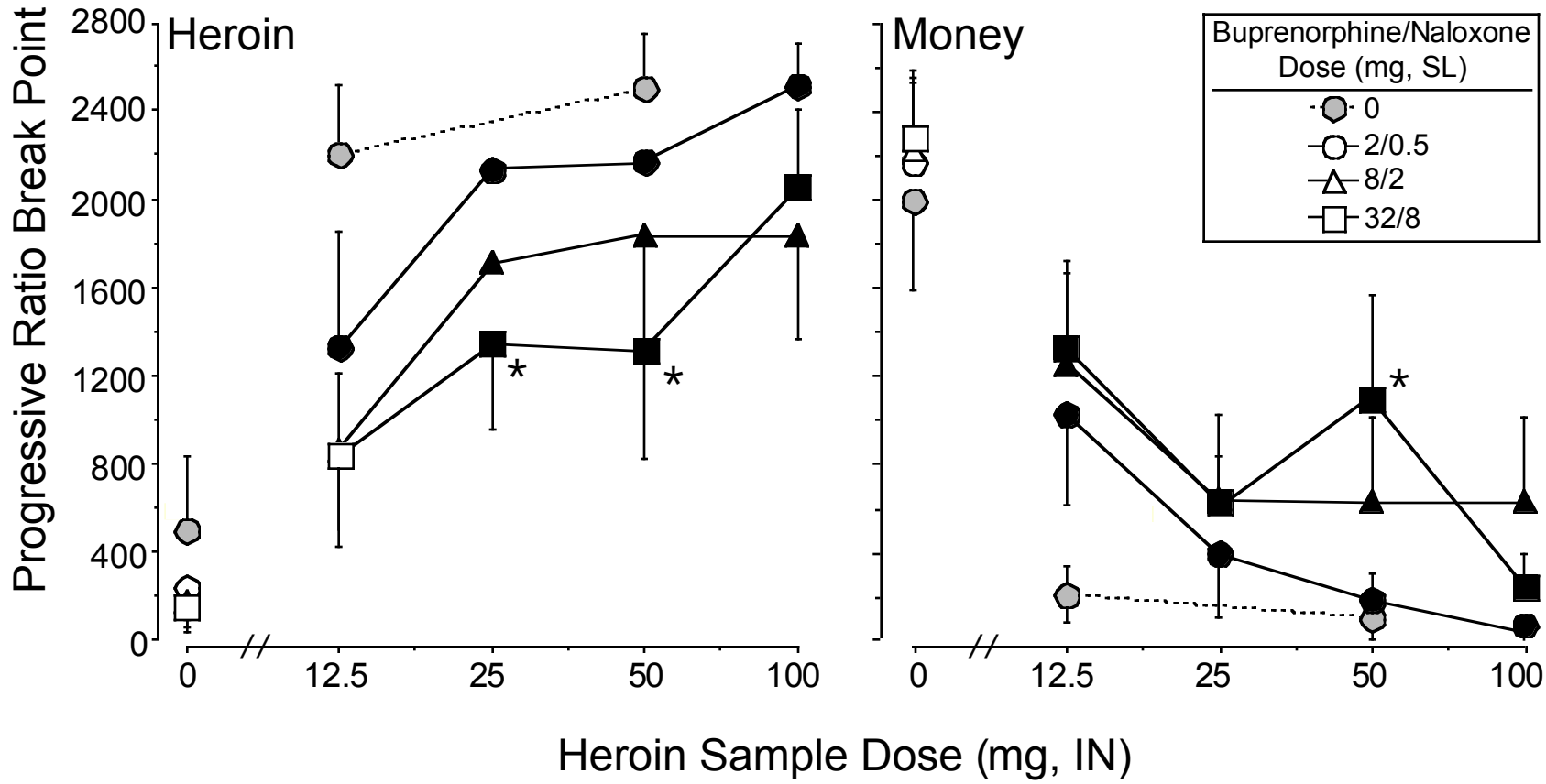
Drug vs Money Choice Procedure

Is it valid?

Evidence

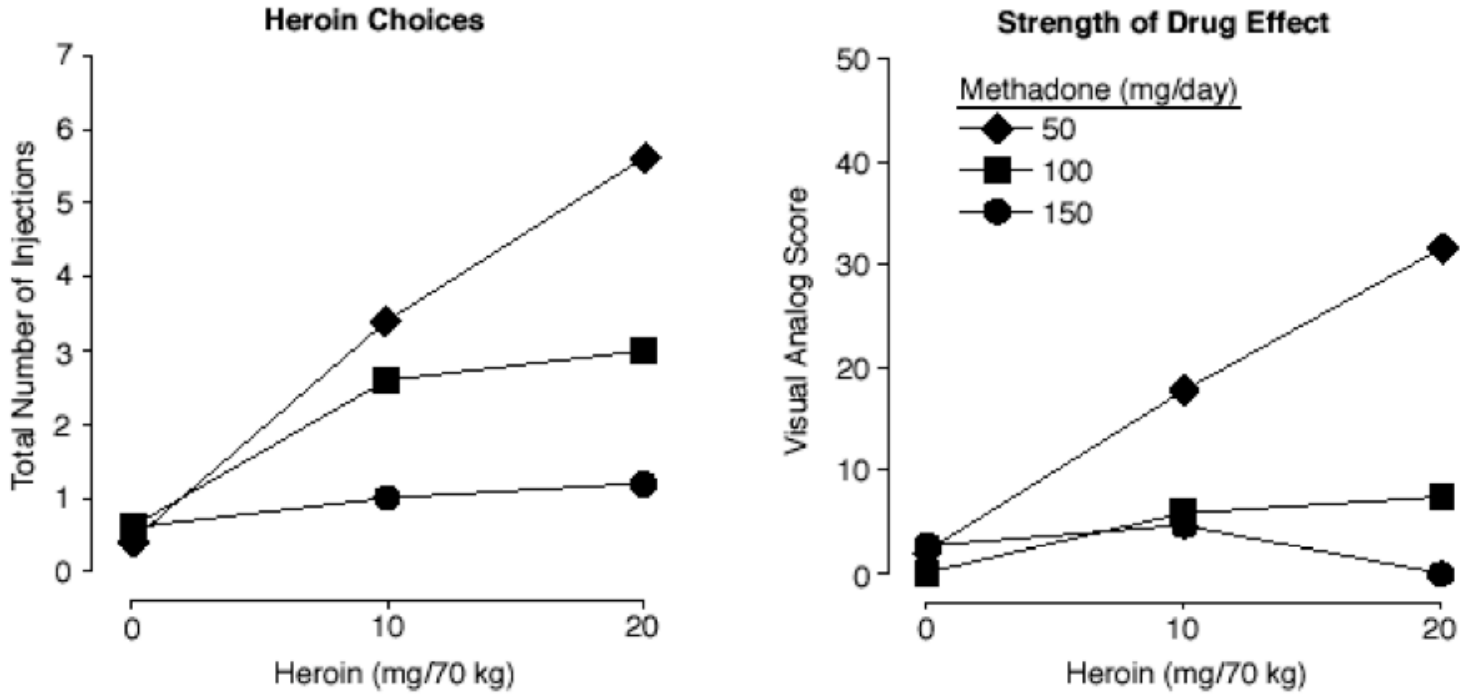
- Maintenance therapies for opioid dependence
  - Buprenorphine
  - Methadone
  - Naltrexone
- Abuse of buprenorphine and the buprenorphine/naloxone combination

Suboxone Maintenance



Comer, Walker & Collins (2005) Psychopharm 181: 664-675

Methadone Maintenance



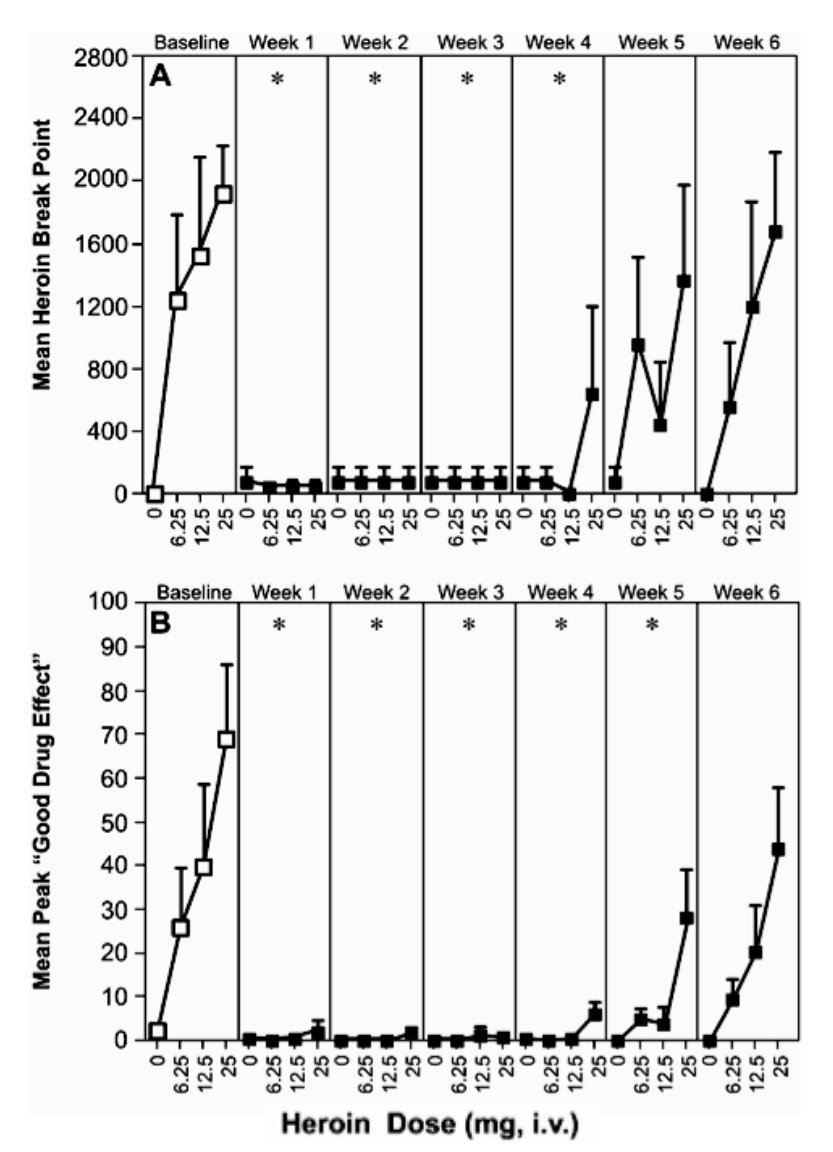
Donny et al. (2005) Addiction 100: 1496-1509

Suboxone and Methadone Clinical Treatment Trial Outcomes

Study [design details]	Treatment (mg od)	Duration	No. of pts	Opioid-negative urine samples[a] (%)	Adjusted mean opioid craving score (VAS score at wk 4[b])	Retention in treatment (% of pts[74,76] or mean time [wk][75])
Comparison with placebo						
Fudala et al.[11,74][c]	BUP/NAL 16/4	4 wk	109	17.8*[d]	29.8*[d]	84[e]
[r, db, mc]	BUP 16		105	20.7*[d]	33.0*[d]	85[e]
	PL		109	5.8[d]	55.1[d]	79[e]
Comparisons with methadone						
Kakko et al.[76] [r, db → sb, mc][f]	BUP/NAL-based stepped care[g] 16/4 to 32/8	6 mo	48	≈78[h]		≈77[d,h]
	MET 70–120		48	≈86[h]		≈79[d,h]
Kamien et al.[75]	BUP/NAL 8/2	17 wk	82			12.1
[r, db, sc]	BUP/NAL 16/4		58			13.2
	MET 45		52			12.5
	MET 90		76			12.3

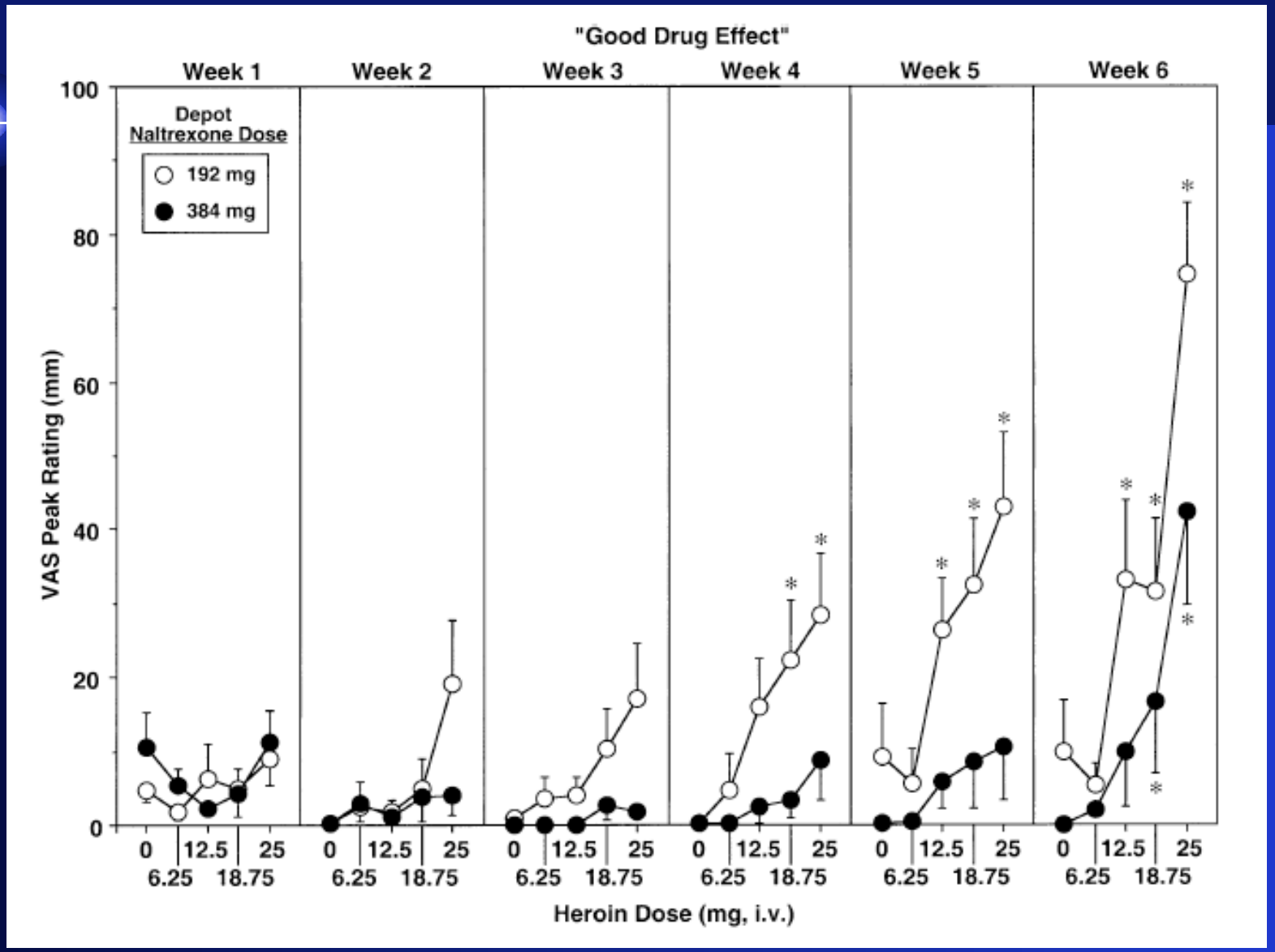
Orman & Keating (2009) Drugs 69(5): 577-607

Naltrexone Maintenance



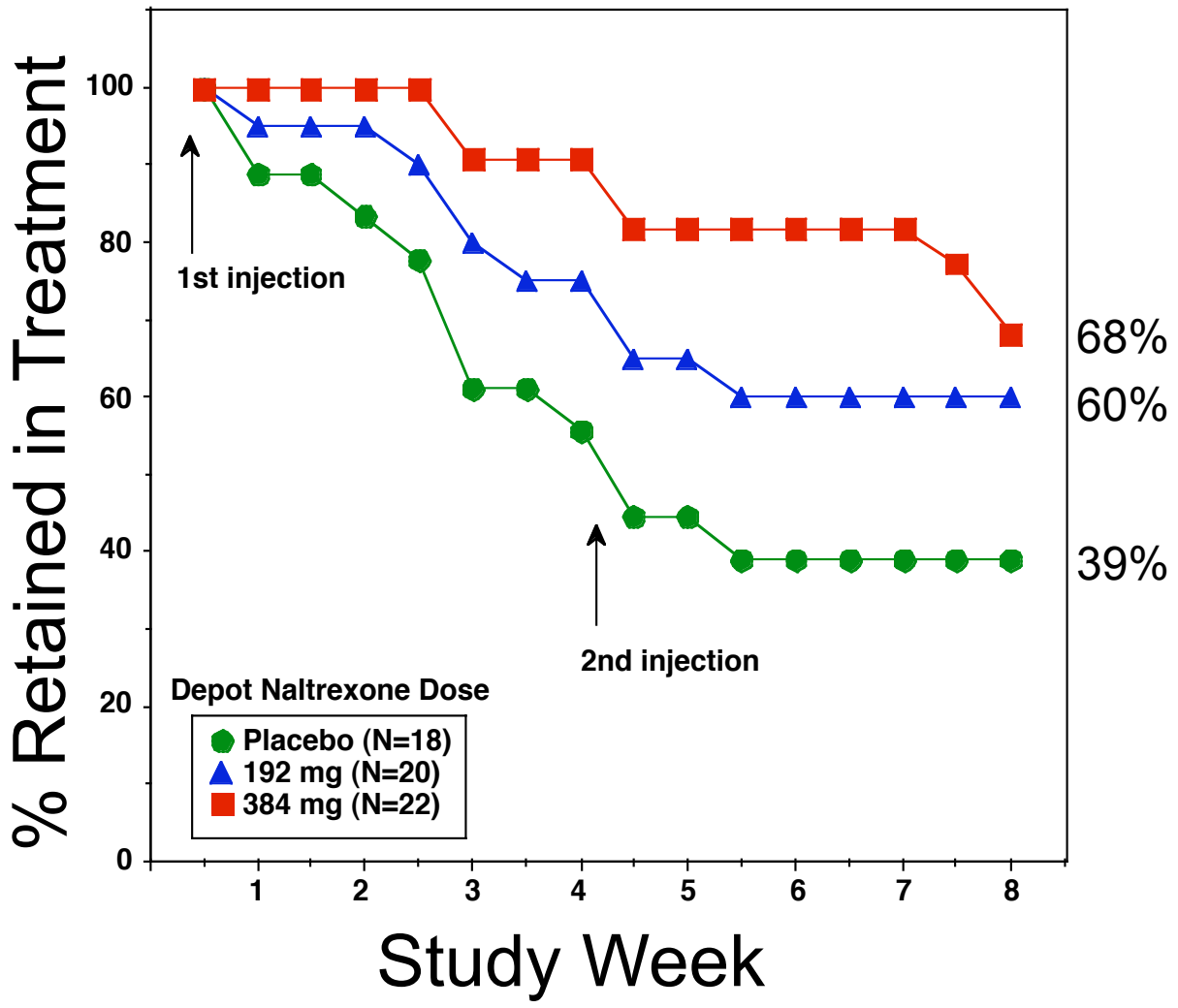
Sullivan, Vosburg & Comer (2006) Psychopharm 189: 37-46

Naltrexone Maintenance



Comer et al. (2002) Psychopharm 159: 351-360

Depot Naltrexone Maintenance



Comer et al. (2006) Arch Gen Psychiatry 63: 210-218

IV Buprenorphine Abuse

Drug and Alcohol Review (March 2008), 27, 197–199

BRIEF COMMUNICATION

Buprenorphine injection

CAMPBELL K. AITKEN, PETER

Macj

The American Journal of Drug and Alco
Copyright © Informa Healthcare USA, I
ISSN: 0095-2990 print / 1097-9891 onli
DOI: 10.1080/00952990802122259

Case Series of I in Kuala

R. Douglas Bruce, M.D.,
Laurie Sylla, M.A
Adeeba Kamarulzaman,
[1]AIDS Program, Section of Infectic
New Ha
[2]Community Health Center of
[3]Infectious Diseases Unit
Kuala

ELSEVIER

Drug and Alcohol Dependence 69 (2003) 175–181

DRUG and ALCOHOL DEPENDENCE

www.elsevier.com/locate/drugalcdep

Intravenous use of prescribed sublingual buprenorphine tablets by

European Addiction Research

Research Report

Eur Addict Res 2007;13:207–215
DOI: 10.1159/000104883

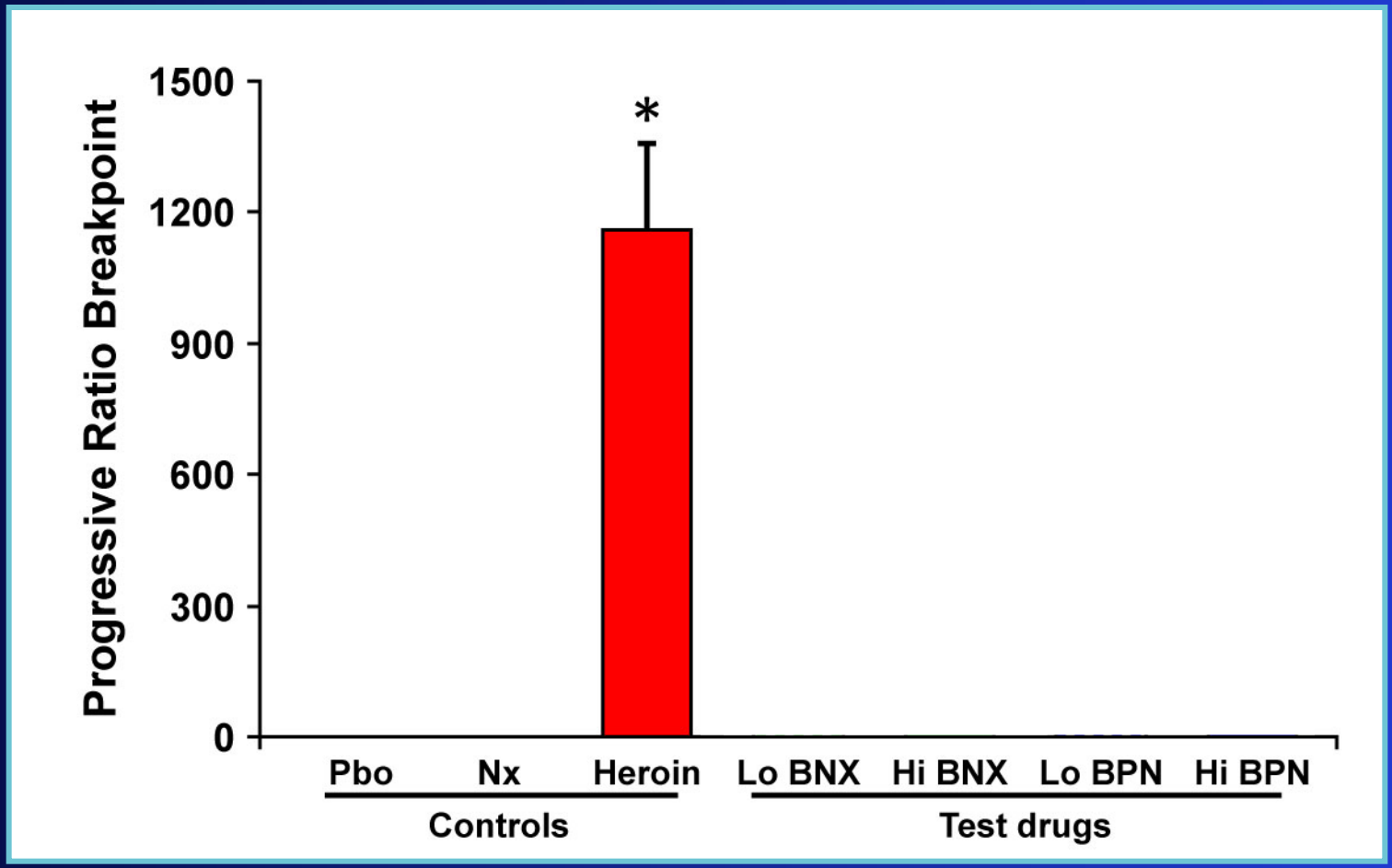
Buprenorphine Misuse among Heroin and Amphetamine Users in Malmo, Sweden: Purpose of Misuse and Route of Administration

A. Hakansson[a] A. Medvedeo[a] M. Andersson[b] M. Berglund[a]

[a]Department of Clinical Alcohol Research, Lund University, Lund, and [b]Department of Infectious Diseases, Malmo University Hospital, Malmo, Sweden

IV Suboxone vs Subutex Self-administration

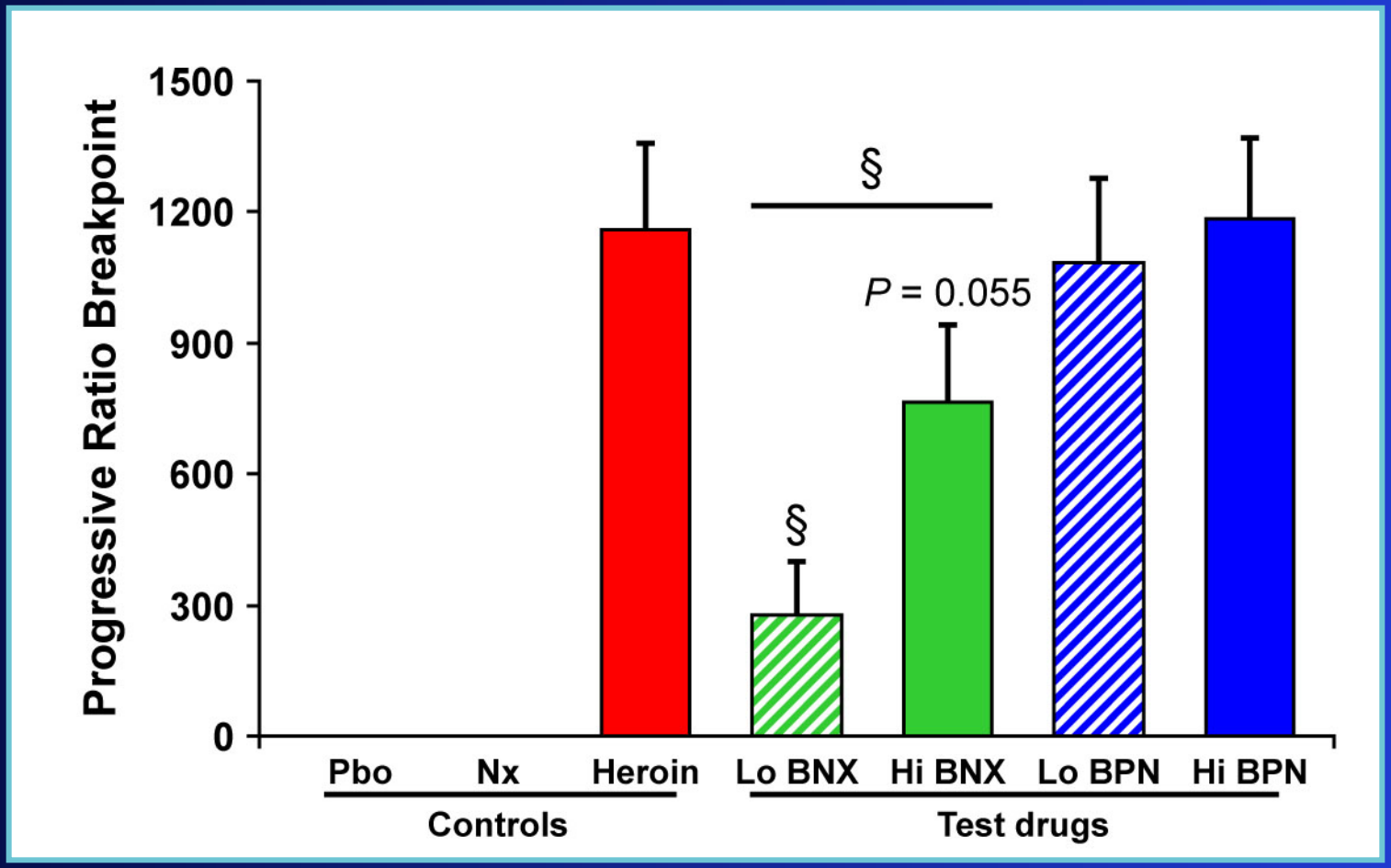
∗ Significant difference from placebo
(*P* <0.0005)



Comer et al. (Under revision) Addiction

IV Suboxone vs Subutex Self-administration

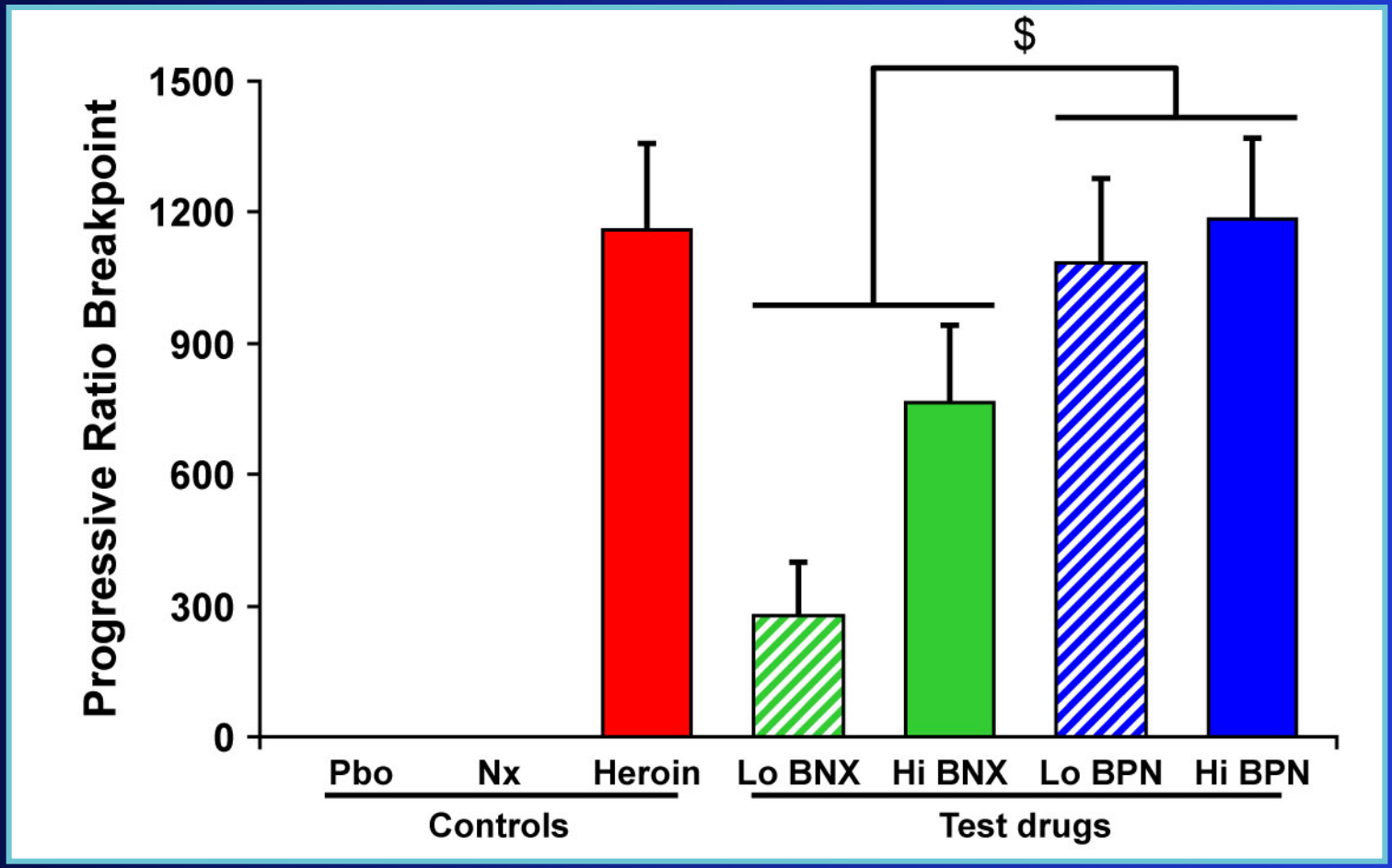
§ Significant difference from heroin
(*P* = 0.0001)



Comer et al. (Under revision) Addiction

IV Suboxone vs Subutex Self-administration

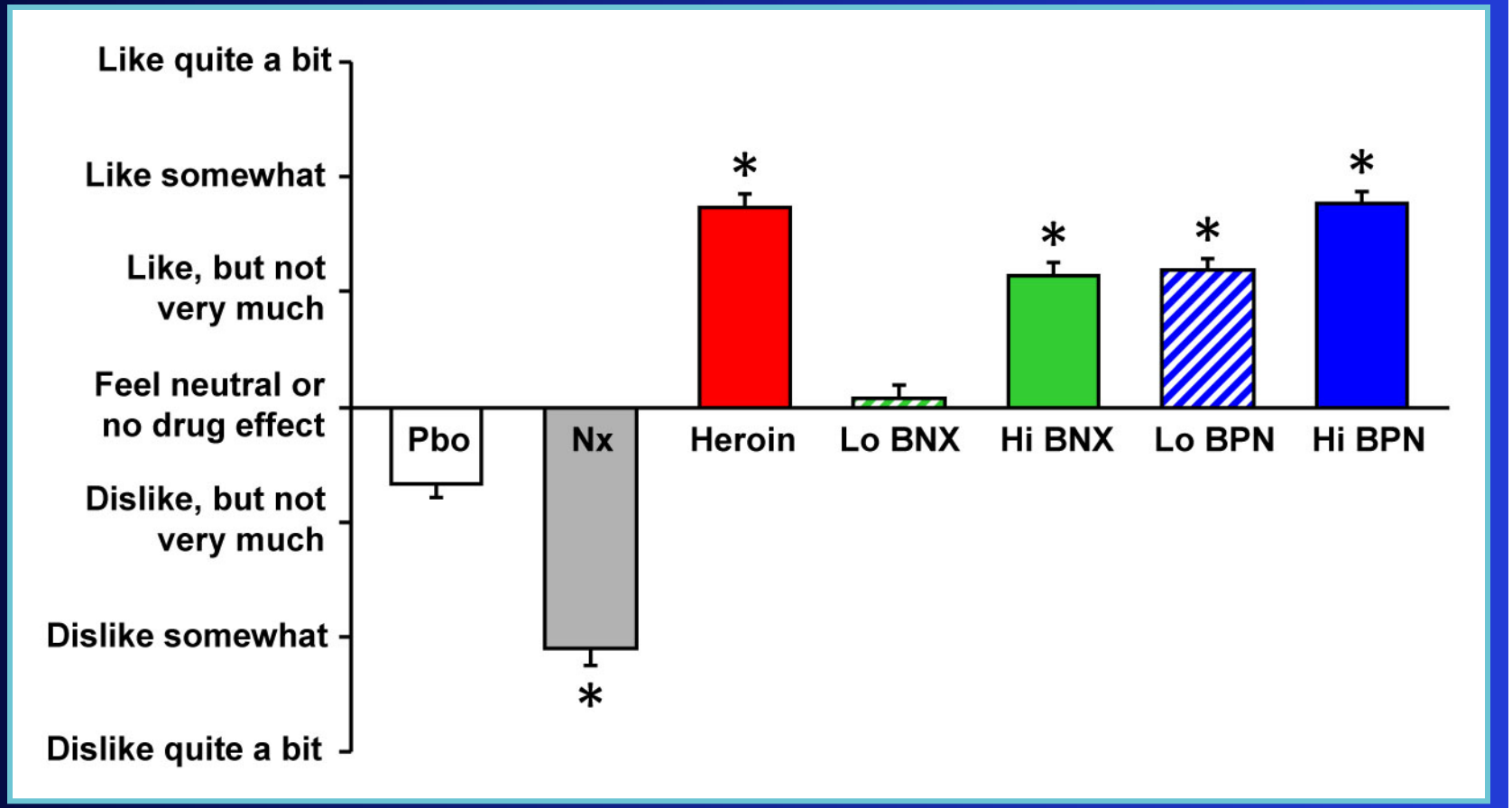
$ Significant difference between BNX and BPN
(*P* = 0.0001)



Comer et al. (Under revision) Addiction

IV Suboxone vs Subutex "Liking"

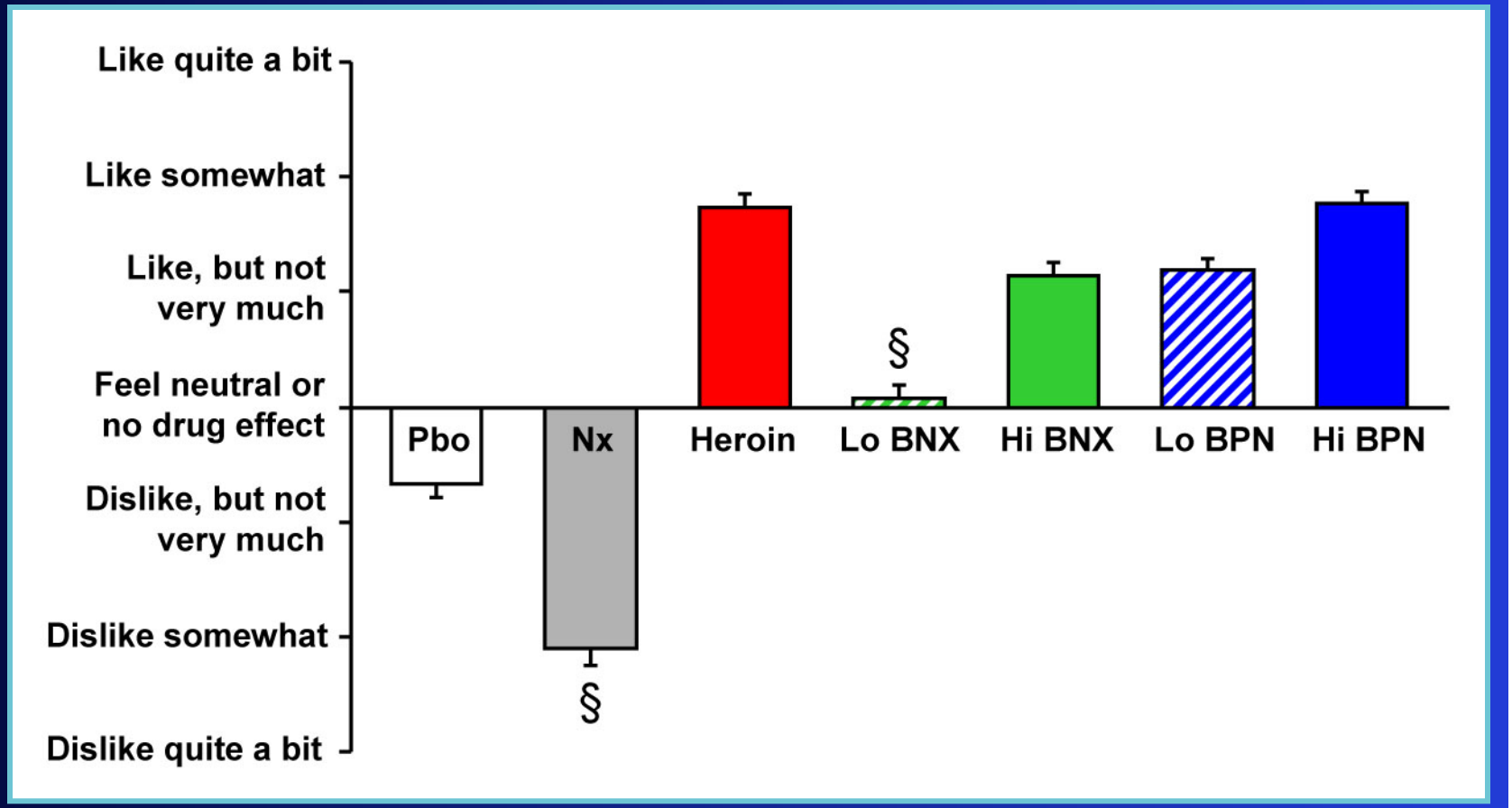
∗ Significant difference from placebo
(P <0.001)



Comer et al. (Under revision) Addiction

IV Suboxone vs Subutex "Liking"

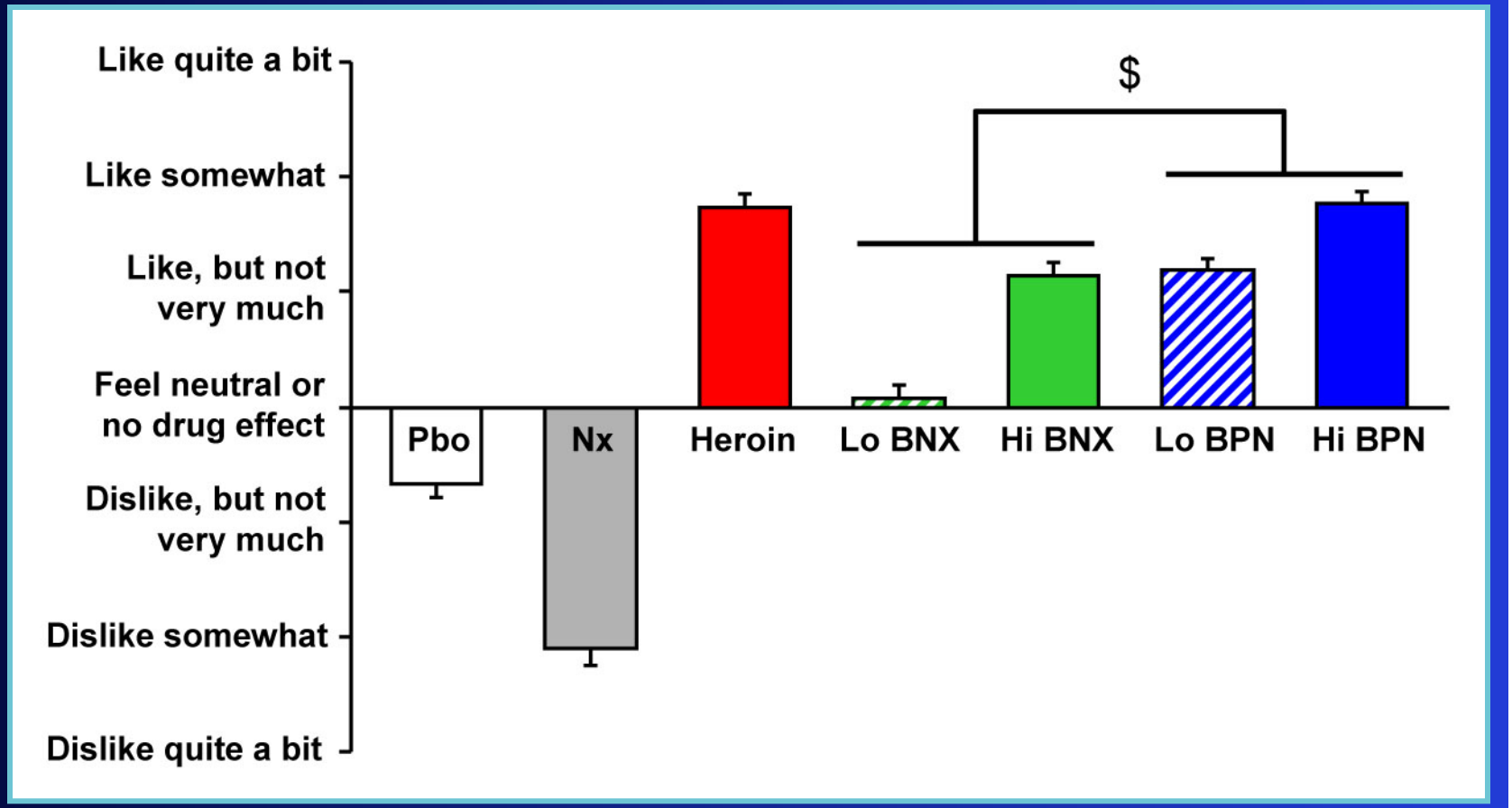
§ Significant difference from heroin
(*P* <0.005)



Comer et al. (Under revision) Addiction

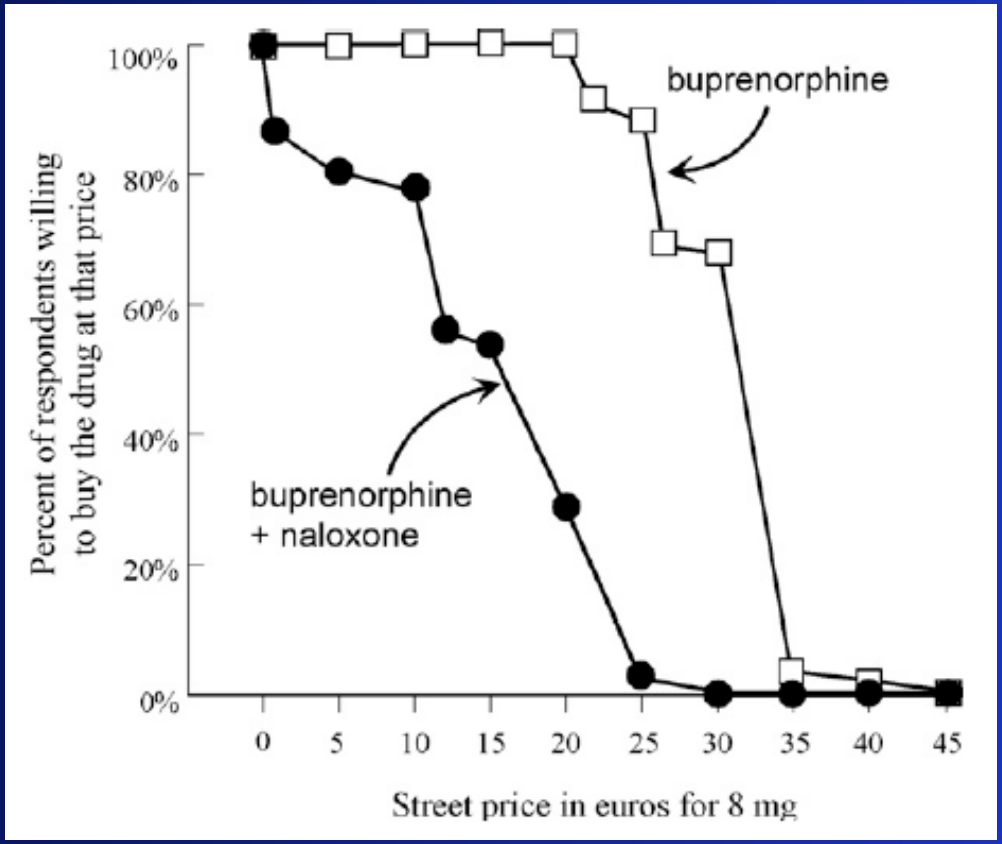
IV Suboxone vs Subutex "Liking"

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



Comer et al. (Under revision) Addiction

Survey Data



Alho et al. (2007) DAD 88: 75-78

Survey Data

The American Journal of Drug and Alcohol Abuse, iFirst:1–5, 2009

ISSN: 0095-2990 print/ 1097-9891 online
DOI: 10.1080/00952990802585406

informa
healthcare

Lack of Reduction in Buprenorphine Injection After Introduction of Co-Formulated Buprenorphine/Naloxone to the Malaysian Market

R. Douglas Bruce, M.D., M.A., M.Sc.
Yale University AIDS Program, New Haven, Connecticut, USA

Sumathi Govindasamy
Center of Excellence for Research in AIDS, University of Malaya, Kuala Lumpur, Malaysia

Laurie Sylla, M.A.
Yale University AIDS Program, New Haven, Connecticut, USA

Adeeba Kamarulzaman, M.D.
Center of Excellence for Research in AIDS, University of Malaya, Kuala Lumpur, Malaysia

Frederick L. Altice, M.D.
Yale University AIDS Program, New Haven, Connecticut, USA

Summary

- A good concordance exists between the reinforcing and subjective effects of opioids in a laboratory setting and “real world” abuse
- BUT, caution is needed for other drug classes…

Medications for Cocaine Dependence

Table 1
Outcomes from drug interaction testing of putative pharmacotherapies against cocaine on subjective effect measures and self-administration

Test agent	Change in subjective responses[a]	Change in self-administration	References
Flupenthixol	–	–	Evans et al. (2001)
Butorphanol	–	–	Walsh et al. (2001)
Phenytoin	–	–	Sofuoglu et al. (1999)
Desipramine	↓/↑	–	Fischman et al. (1990)
Enadoline	↓	–	Walsh et al. (2001)
Gabapentin	↓	–	Hart et al. (2004)
Pergolide	↓	–	Haney et al. (1998)
ABT-431	↓	–	Haney et al. (1999)
Memantine	↑	–	Collins et al. (2006)
Baclofen	-/↓	↓	Haney et al. (2006)
Buprenorphine	↑	↓	Foltin and Fischman (1994)
Ecopipam	↑/-	↑/-	Haney et al. (2001) and Nann-Vernotica et al. (2001)
Modafinil	↓	↓	Hart et al. (2008)

[a] Arrows denote the direction of change whereby subjective responses to cocaine on abuse liability measures were either increased (↑), decreased (↓) or no change was observed (–).

Comer et al. (2008) DAD 96: 1-15

CONCLUSIONS

The “Gold Standard” provides important initial information regarding the potential abuse liability of novel compounds

It sets the stage for subsequent studies that could examine other factors that are important in obtaining a more comprehensive picture of the abuse liability of a compound (e.g., reinforcing effects, repeated drug administration, effects in special populations)

ACKNOWLEDGMENTS

- Marian Fischman, PhD
- Richard Foltin, PhD
- Maria Sullivan, MD, PhD
- Jeanne Manubay, MD
- Eric Collins, MD
- Suzanne Vosburg, PhD
- Ziva Cooper, PhD
- Jermaine Jones, PhD
- Janet Murray, RN
- Claudia Tindall, RN
- William Kowalczyk, BS
- Phillip Saccone, BS
- Joseph Lazar, BS
- Greta Bielaczyc, BS