Addiction Research in Humans: A Forty-Year Career Retrospective

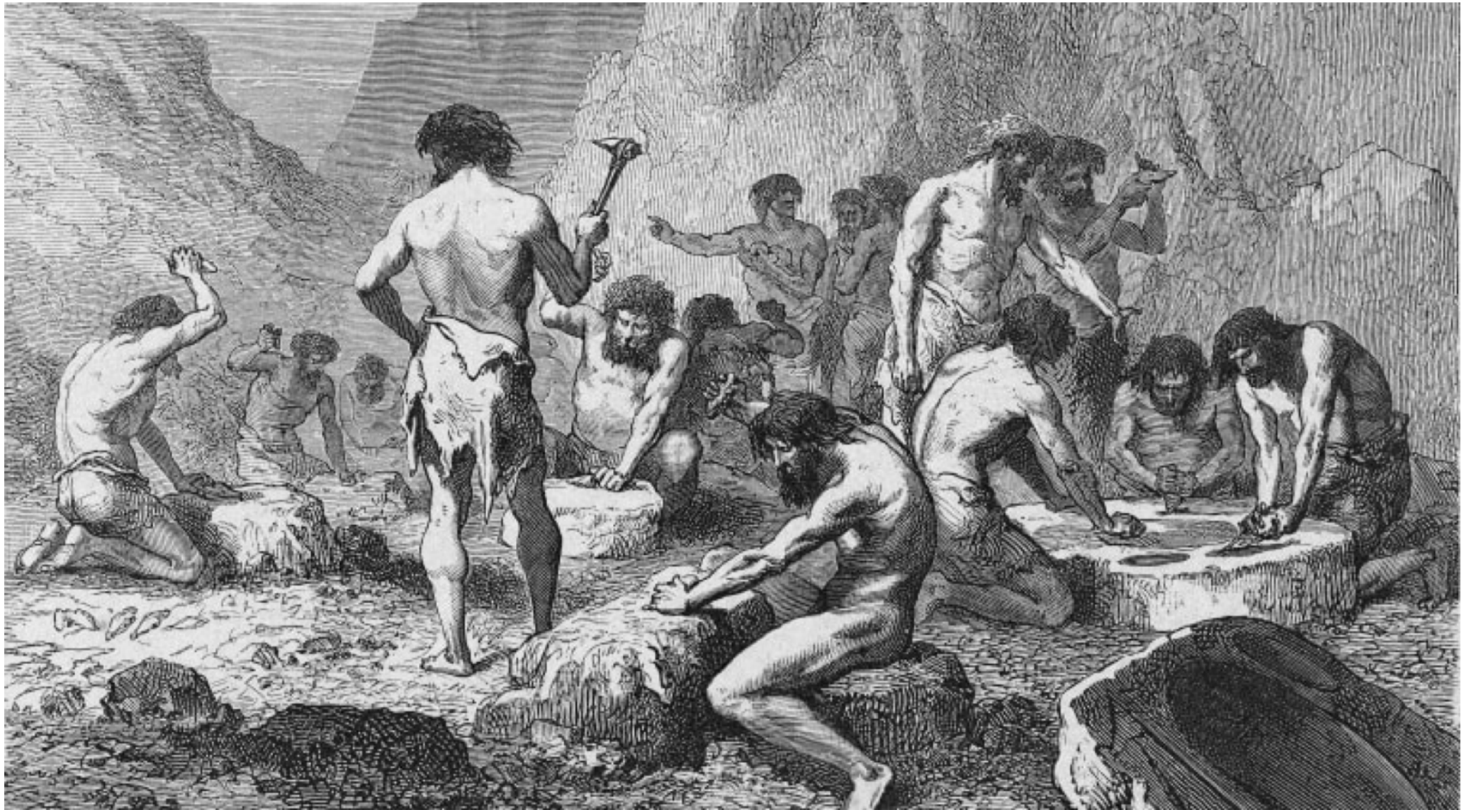
Based on Eddy Award lecture CPDD 2019

Maxine Stitzer

Career outline

- Graduate school- University of Michigan- 1967-1971
  - Behavioral pharm & self-administration- James H. Woods
- Post doctoral research associate- 1972-1974
  - Behavioral pharmacology in squirrel monkeys- James McKearney
- Johns Hopkins University BPRU 1974- 2019
  - George Bigelow, Roland Griffiths

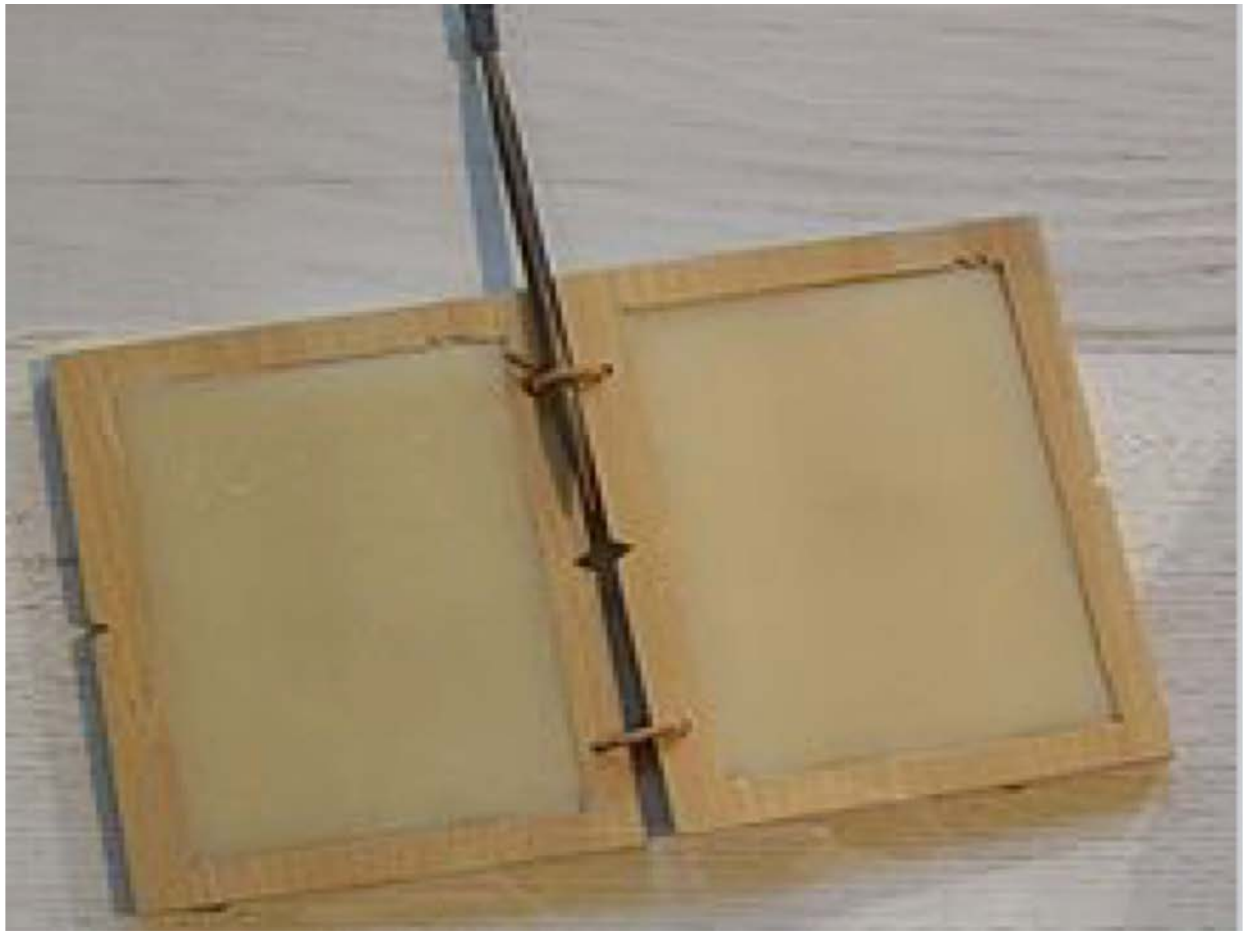
Where we started: 1974



Addiction Research: 1974

- Where things stood
  - Tobacco cigarettes killing people
  - Opiate addiction was endemic
  - Drug addiction as a moral failing; Synanon as model treatment
- Promising starts
  - ARC at Lexington Narcotics Farm characterizing opioid dependence
  - Dole, Nyswander & Kreek re-purposing methadone as a Tx
  - Animal self-administration re-conceptualizing drug taking as biologically reinforced behavior
  - Beginning attempts at controlled human research (e.g. Mendelson & Mello)

Lots of Research Opportunity



BPRU: Setting and Resources

- 14-bed fully staffed residential research unit
- Small (N = 90 patients) methadone maintenance research clinic
- T-32 postdoctoral training program
- Inspiring colleagues (Bigelow & Griffiths, Joe Brady)
- Collaborative team approach & shared resources
- Rising NIH budget

Forty Four years later: My research perspective in the rearview mirror

- Opioid physical dependence
- Opioid treatment medication
- Behavior therapy: Contingency management

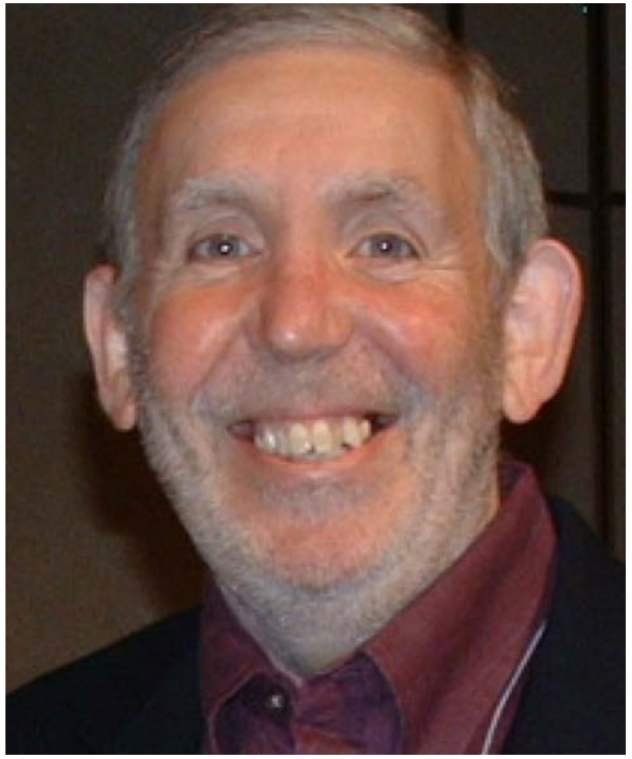
Review accomplishments with comments on future directions

Part 1: Opiod Physical Dependence

Physical dependence is a key aspect of opioid pharmacology & barrier for abuse-free pain medications

How does physical dependence develop?
How long does it take?
Conditions for escalation?

Holtzman animal studies showed opioid physical dependence begins with first exposure



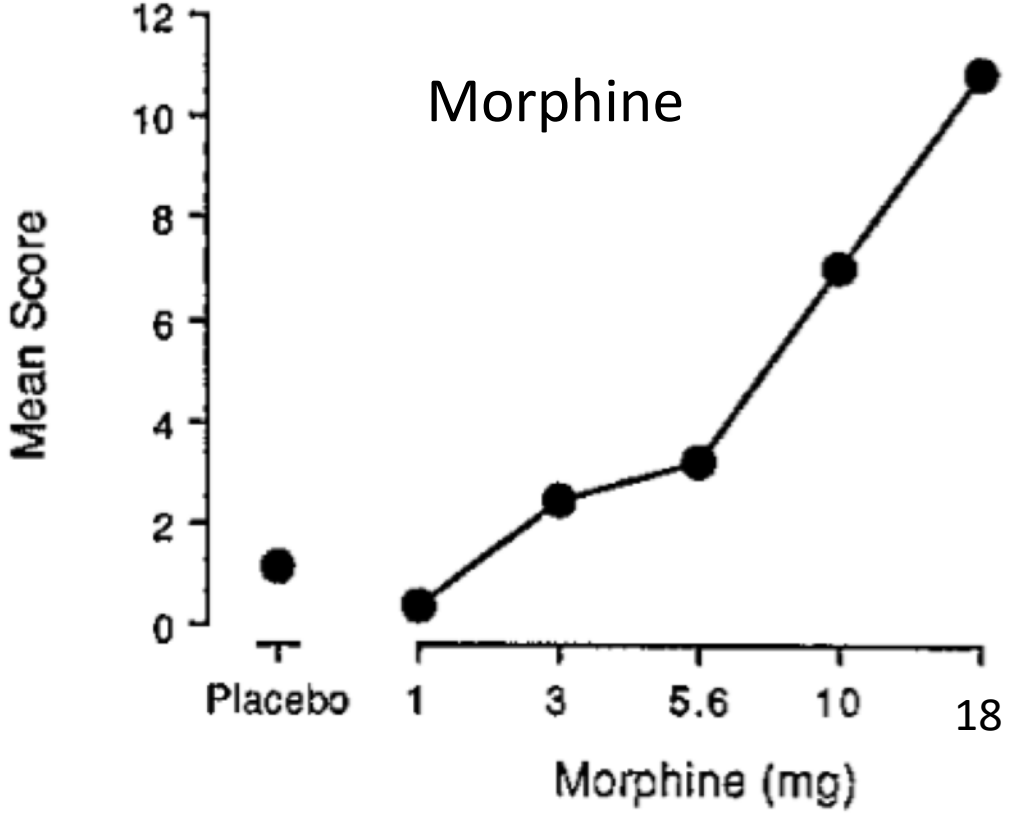
Acute physical dependence in humans

Steve Heishman, Warren Bickel, Kim Kirby, Mark Greenwald, Curtis Wright

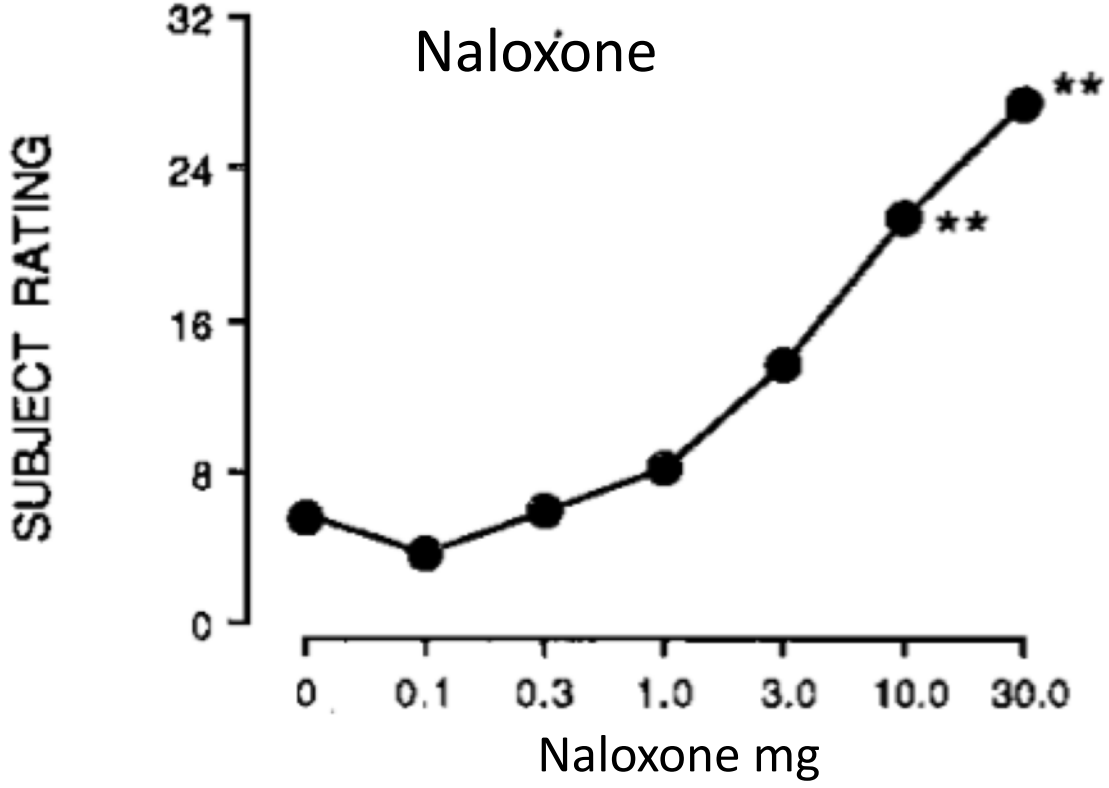
- Question: What are dosing and temporal parameters of opioid physical dependence development in humans?
- Tool: naloxone-challenge to precipitate and “unmask” subclinical withdrawal symptoms
- Strategy: manipulate agonist & antagonist doses & inter-dose temporal window

Challenge dose-effects @ 6-hour spacing interval

Withdrawal symptom ratings

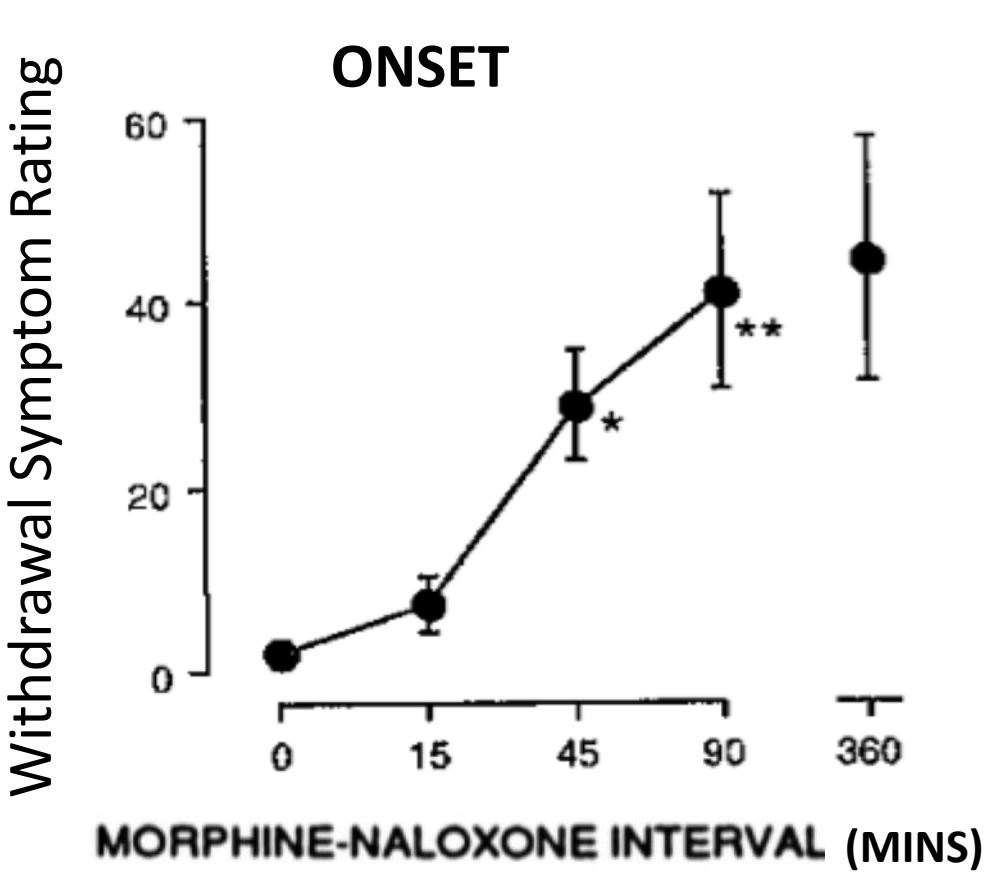


Bickel et al. JPET, 1988

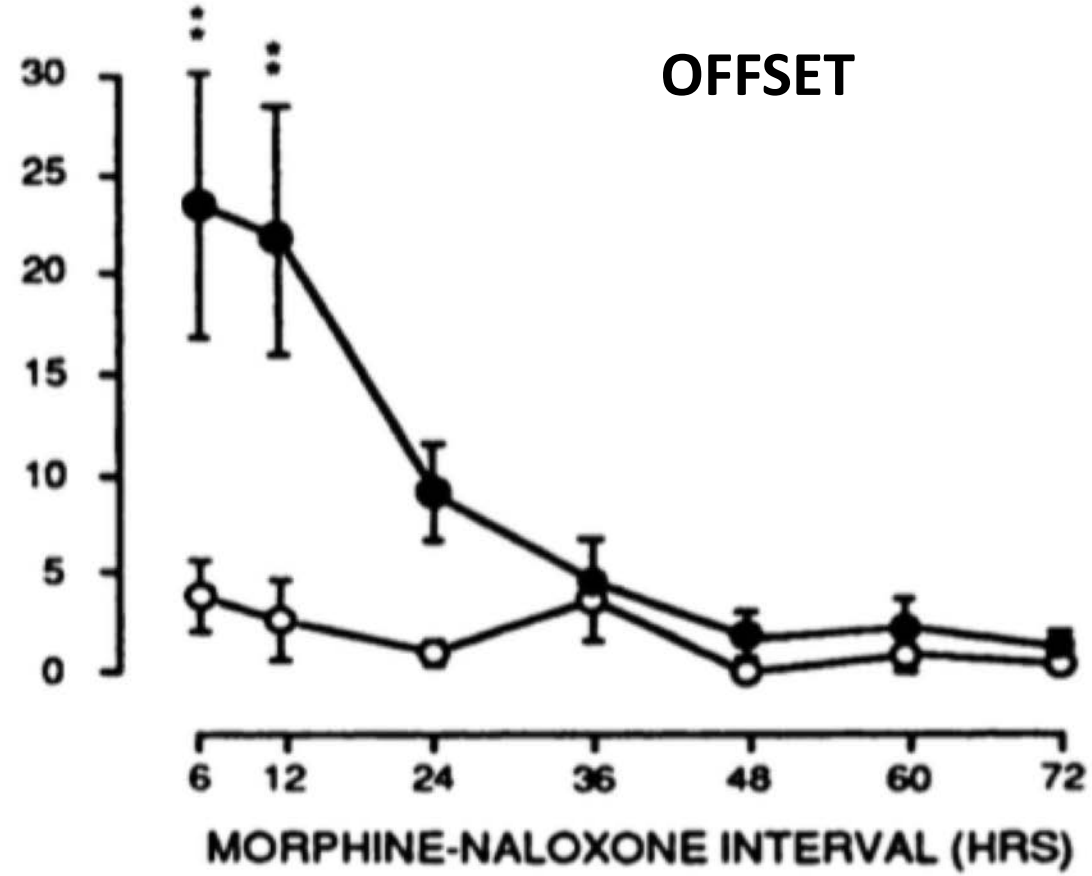


Heishman et al., JPET, 1989)

NALOXONE (10 MG) PRECIPITATED WITHDRAWAL AFTER MORPHINE (18 MG) PRE-TREATMENT



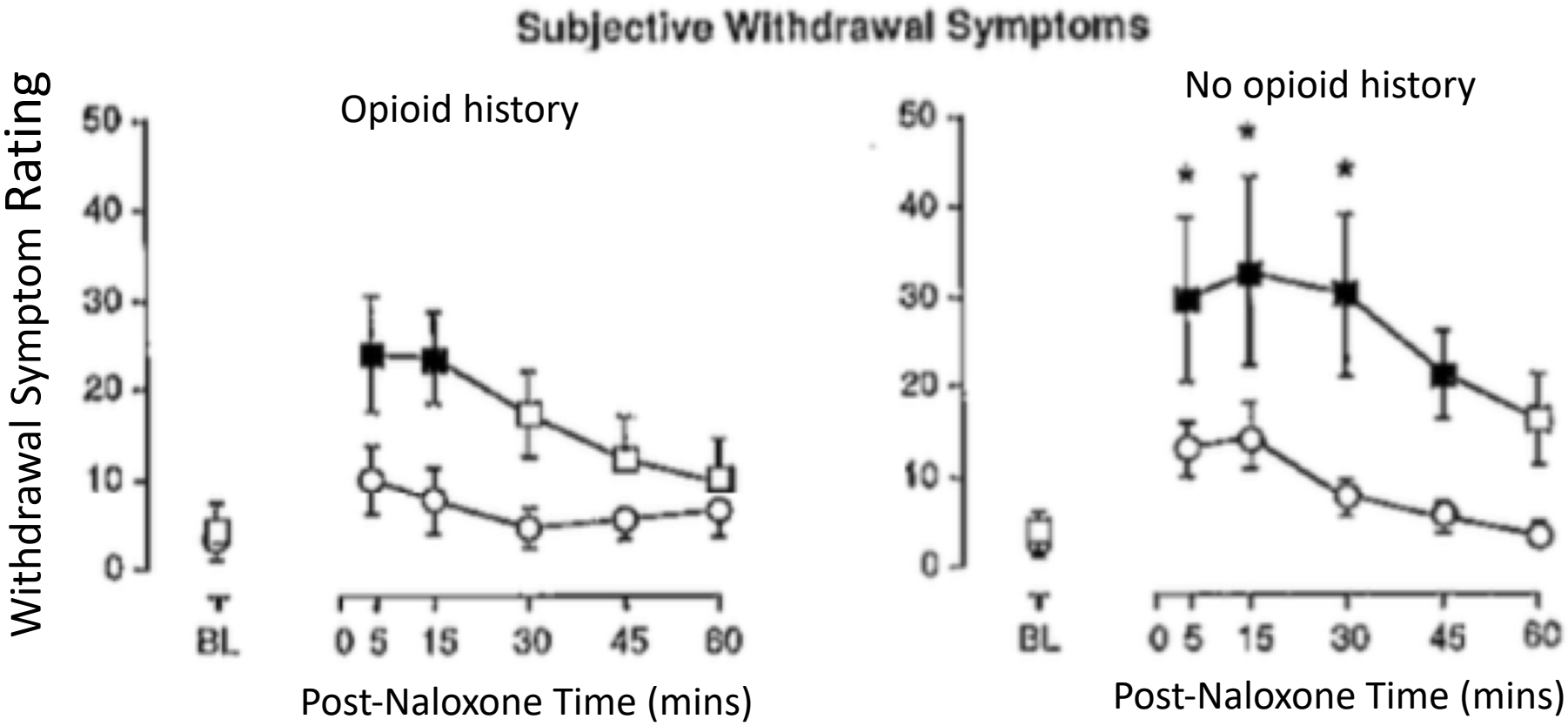
Heishman et al., JPET 1989



Kirby et al. JPET, 1990

Dependence escalation with 1 vs 2 morphine pre-treatments

Naloxone challenge @ 24 hrs after last morphine exposure



Azorlosa et al., Psychopharm, 1994

Opioid physical dependence in humans

- Acute dependence demonstrated with quick onset and lingering offset
- Escalation observed when morphine inter-dosing intervals were 24 hours or less but not If intervals were > 24 hours (chipping)
- Since PD changes last longer (12-24 hrs) than agonist effects, users may be unaware that there is a danger of escalation even with daily agonist exposure intervals
- Lingering questions: What are parameters of physical dependence escalation with modern pain meds including dosing parameters for detection of “spontaneous” withdrawal?

Part 2: Opioid Treatment Medication Studies

- Once physical dependence develops, medication assisted treatment is recommended
- Methadone was in use at clinical Tx centers but doses were often low (e.g. $\leq$ 50 mg/day)
- Our studies explored optimal methadone dosing parameters in the methadone clinic

Methadone dose effects in clinical practice

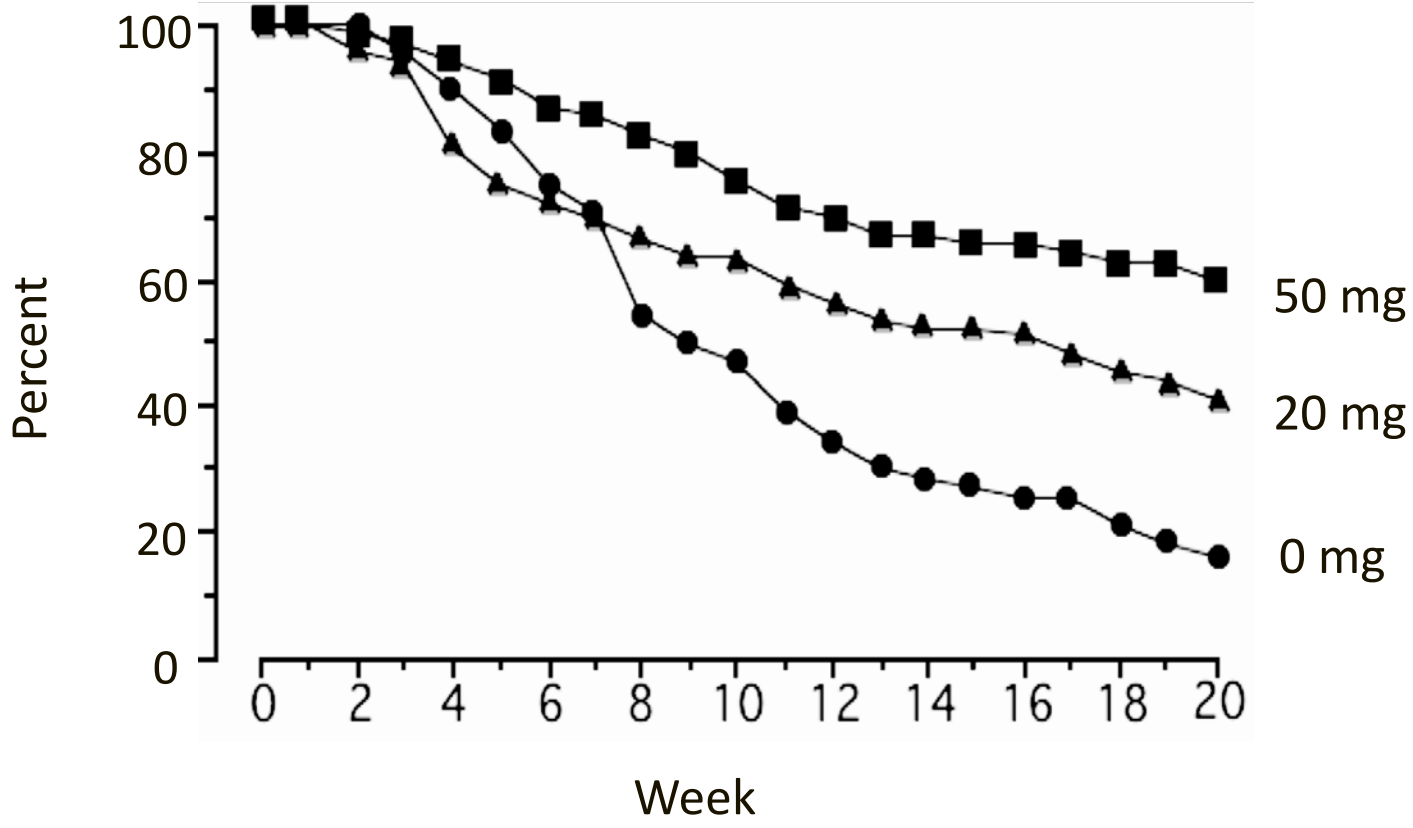
Strain et al., 1993

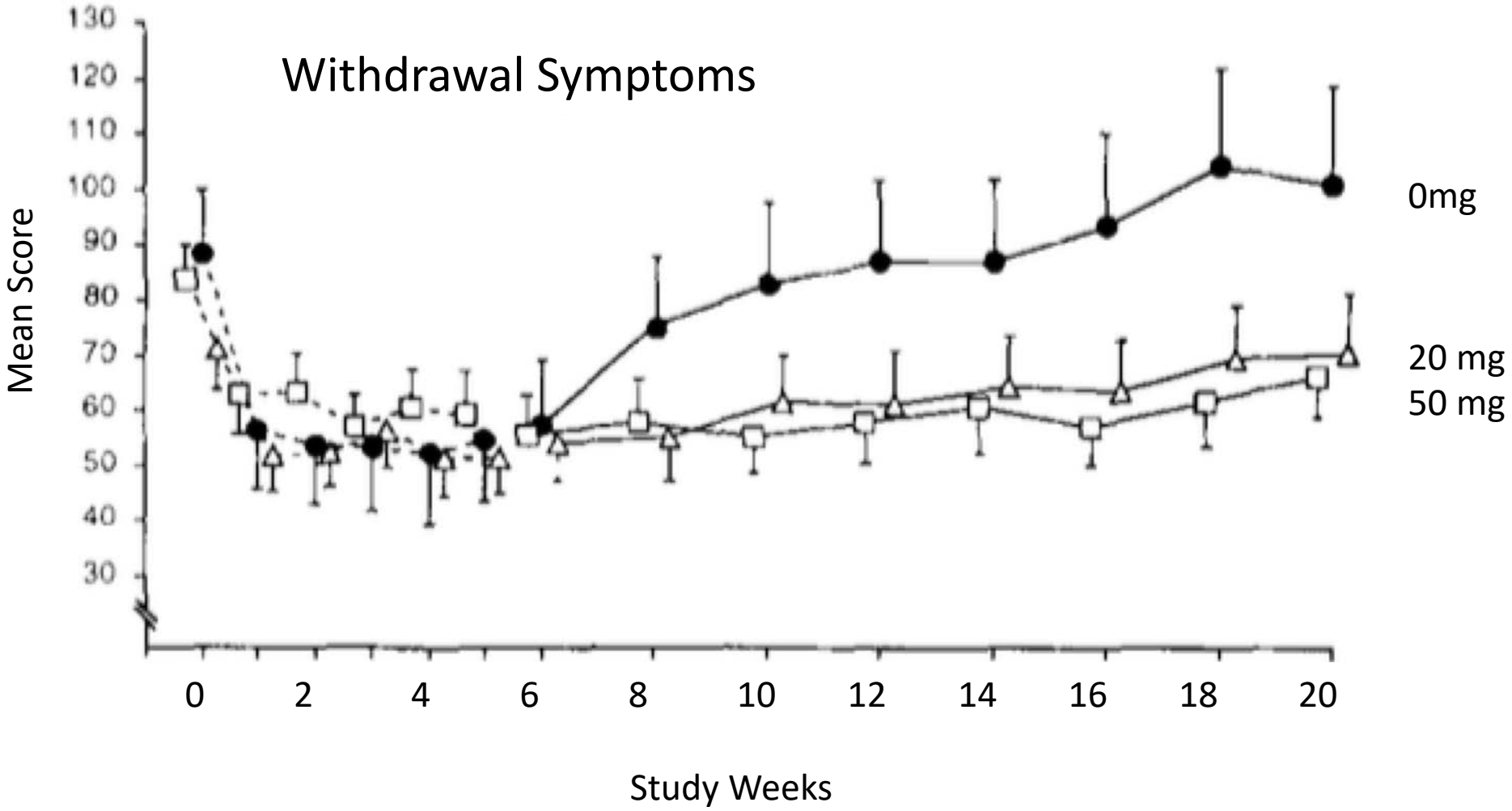
20-week study. N = 60

Random assignment to: 0, 20 or 50 mg

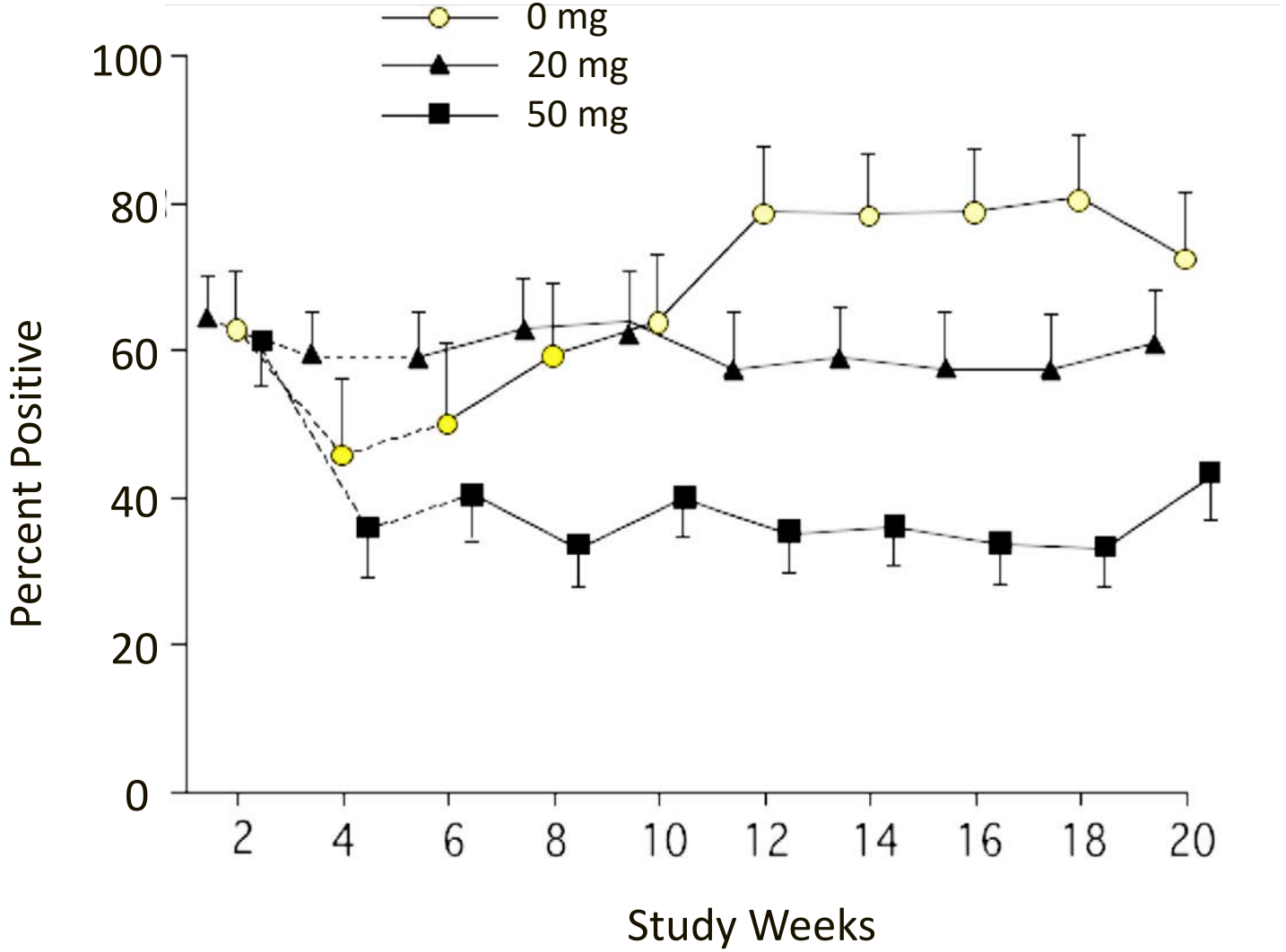
0 mg = 6 week taper followed by placebo

Treatment Retention




Withdrawal Symptoms
Mean Score
130
120
110
100
90
80
70
60
50
40
30
0
2
4
6
8
10
12
14
16
18
20
Study Weeks
0mg
20 mg
50 mg

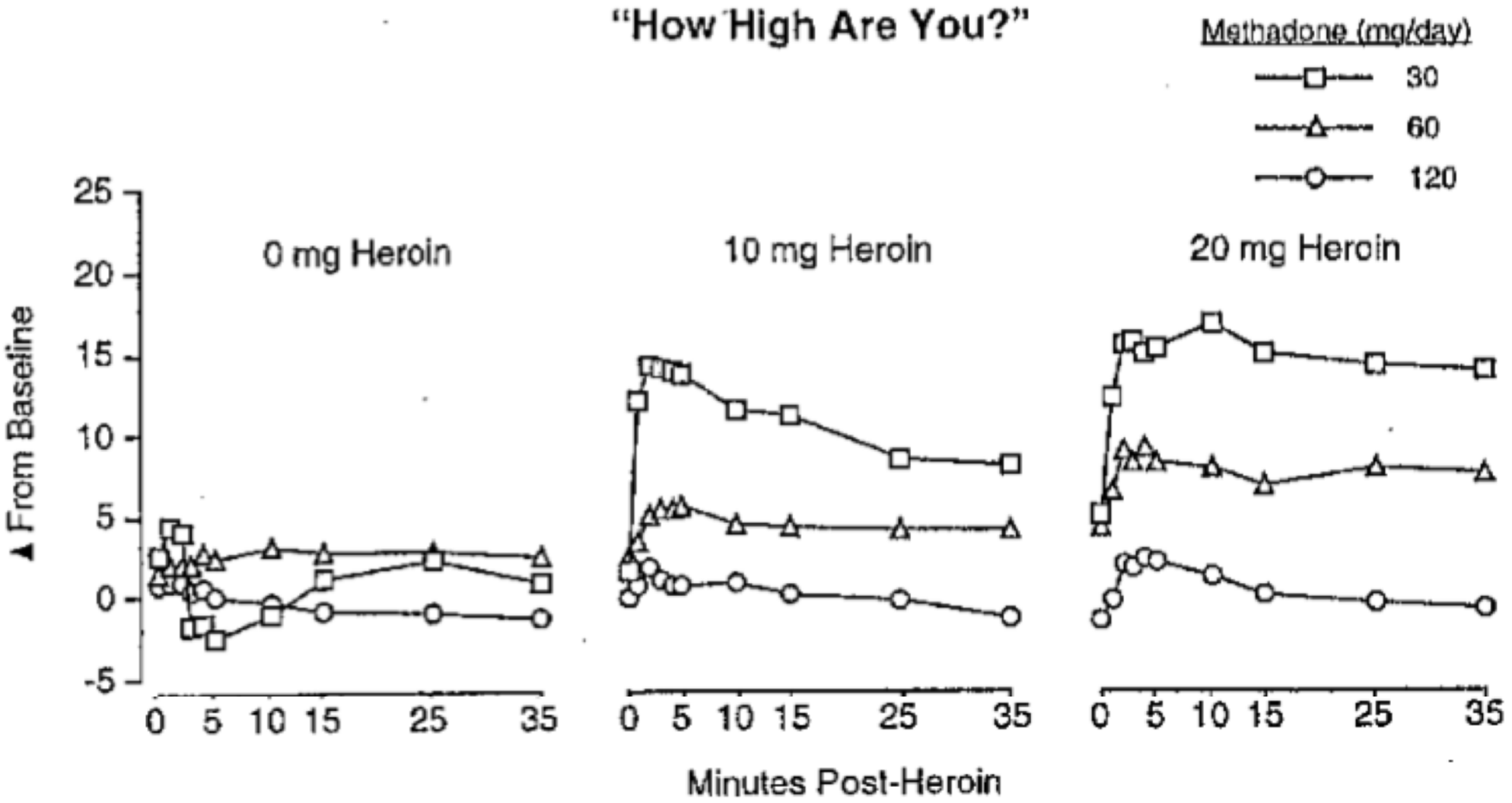
Percent Opioid Positive Urines:



Took studies into residential research setting to examine opioid blockade with higher dose methadone

Methadone Blockade: 30, 60 & 120 mg

Donny, Walsh et al. 2002



Medication Treatment Research

- Careful parametric research supported effectiveness of higher methadone doses
- Withdrawal suppression at low doses allows these to be used but doses of >100mg are needed to effectively block subjective opioid agonist effects
- Dosing practices did change with higher doses becoming standard

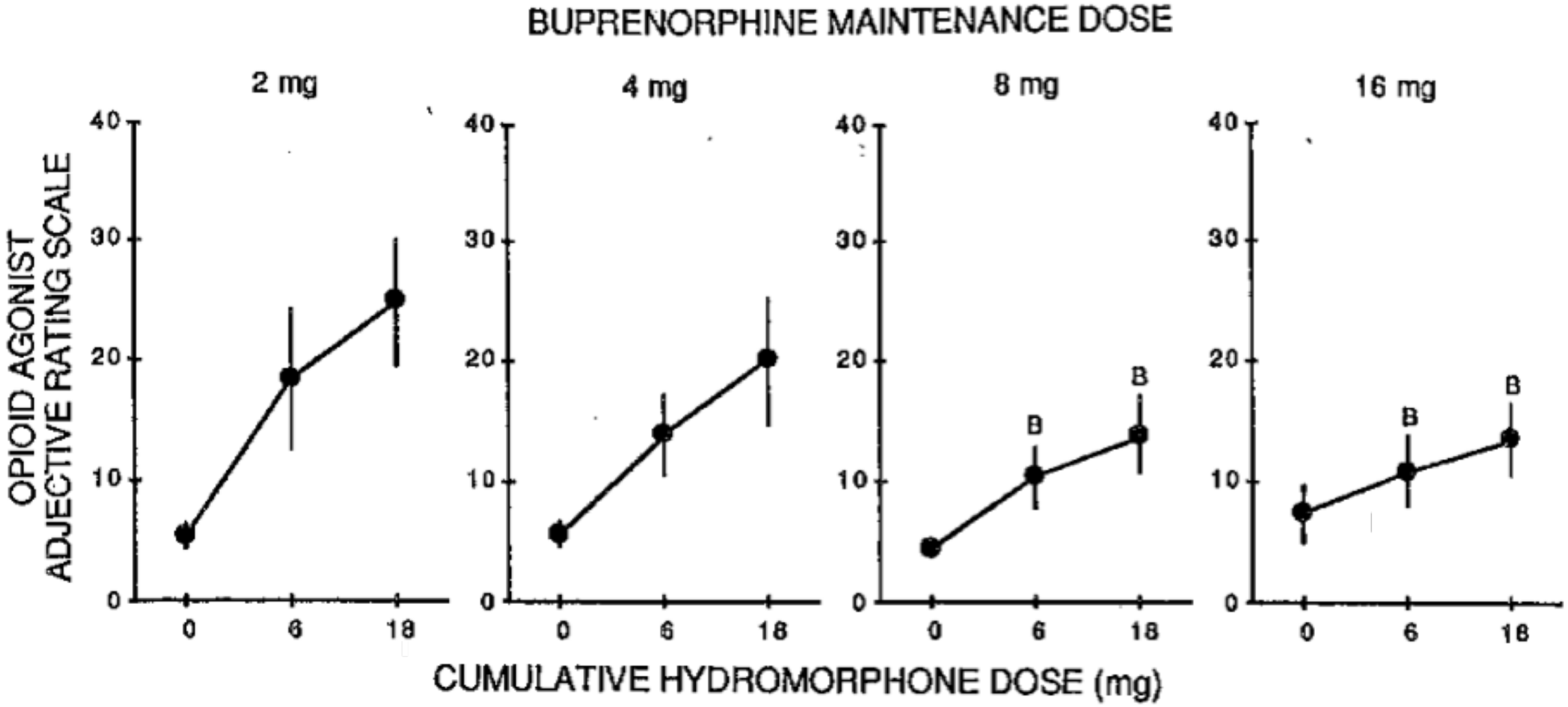
Medication development: Buprenorphine safety and efficacy

- Seminal and pivotal research done at BPRU
- Leaders included Ed Johnson, George Bigelow, Sharon Walsh, Eric Strain

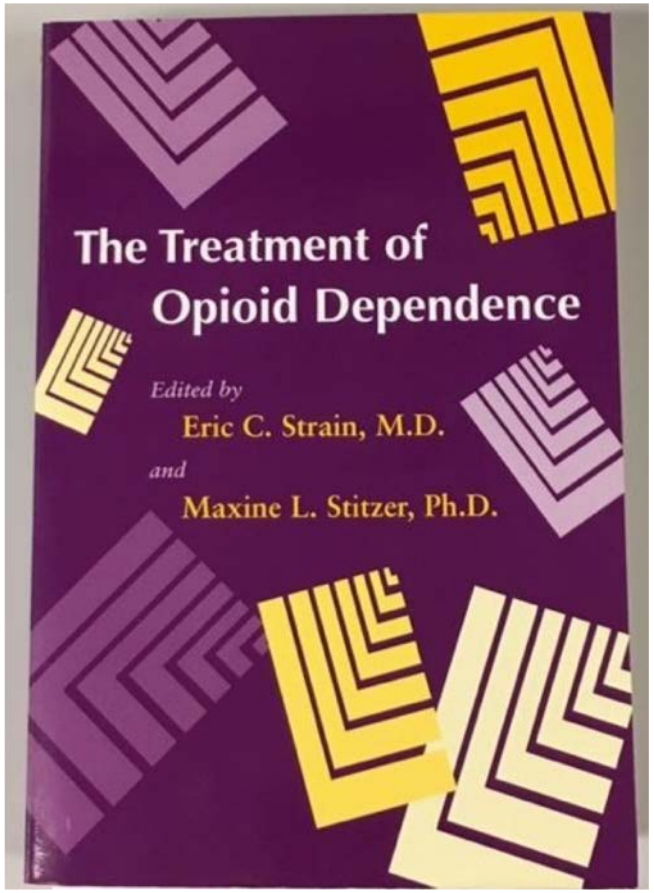
- Careful laboratory work characterized pharmacology
- Clinical trials showing efficacy equivalent to methadone
- Studies provided data for FDA approval

Buprenorphine dose-related blockade

Bickel, Johnson et al., JPET 1988



Medication Treatment Research



OUD treatment medications: Lingering questions

- How can treatment be made more accessible and more engaging?
  - Expand treatment capacity
  - Reduce treatment burden using novel low threshold approaches
  - Address attitudes and stigma

- How can treatment be improved and benefits extended over time?
  - Dosing parameters
  - Drop-out reduction interventions
  - New aftercare models

Opioids are not the only problem

Cocaine epidemic of the 1990's fueled need for effective behavioral treatments

Motivational Interviewing: Bill Miller

Cognitive-Behavior Therapy: Alan Marlatt

Maxine & George: Pioneers in Contingency Management

Part 3: Contingency Management (CM)

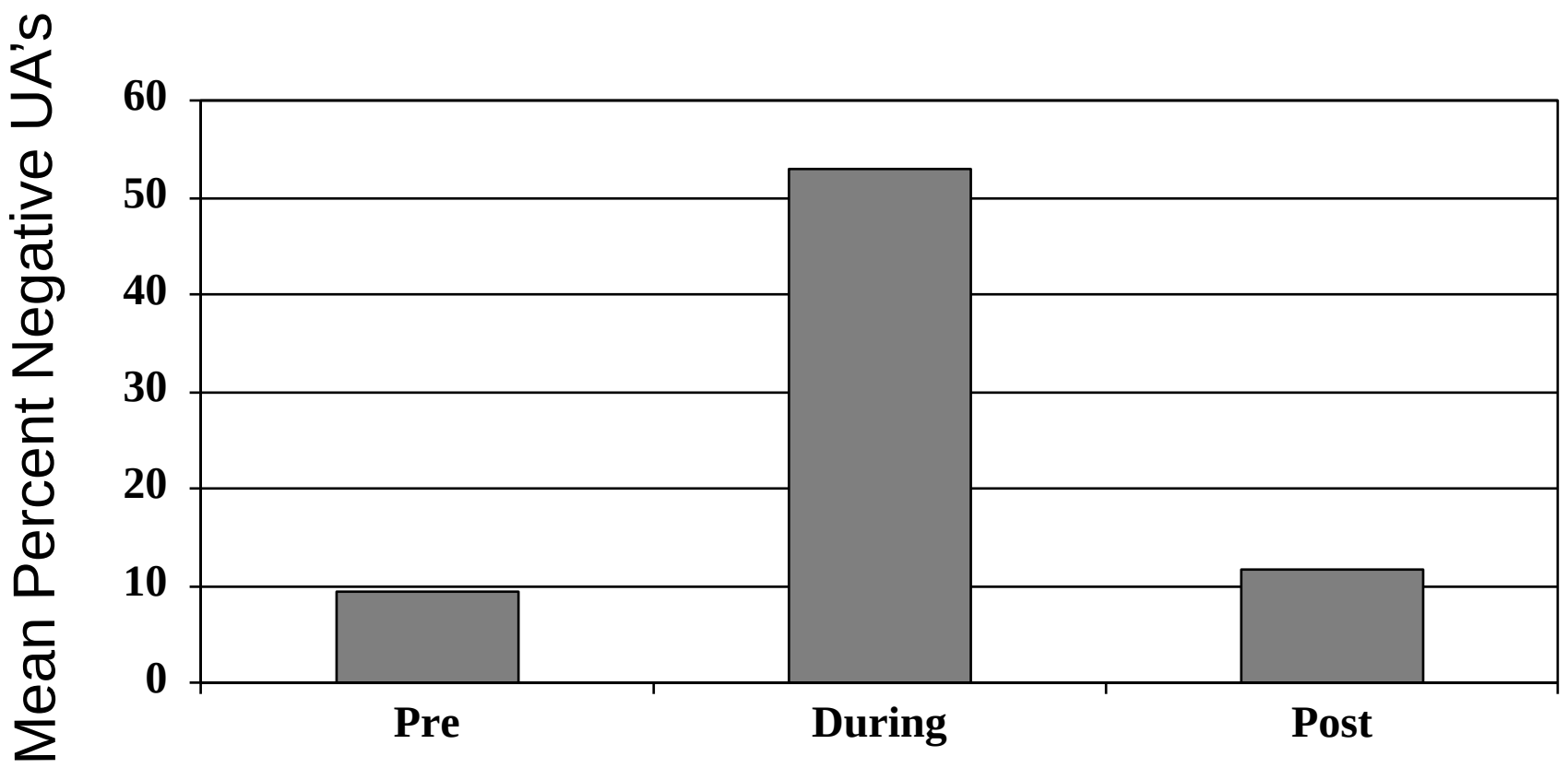
Inspired by behaviorism of BF Skinner and recognition from animal self-administration that drug-seeking is biologically reinforced, BPRU pioneered application of CM to the clinical problem of drug addiction

History Of CM AT BPRU

- Noted that methadone maintenance patients were using benzos and cocaine during treatment
- Urinalysis testing provided objective marker of recent drug use vs abstinence
- Positive reinforcement for abstinence might counter drug reinforcers
- Drug-negative urine set occasion for delivery of positive reinforcement
- Reinforcers identified were money & take-homes

Percent Benzodiazepine Negative Urines During a 3-month Intervention (N = 10)

(Stitzer, Bigelow, et al. JABA, 1982)



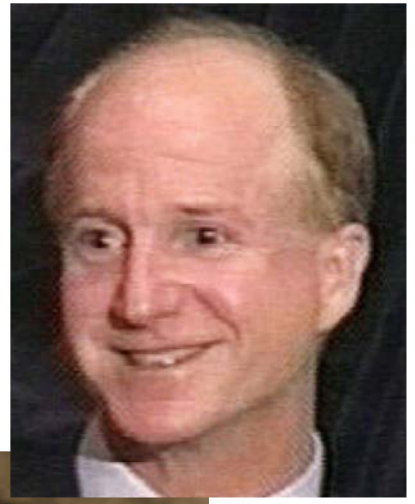
Small proof of concept studies

- Various drug targets
  - Opiates, cocaine, benzos, tobacco smoking
- Various reinforcers
  - Money, take-homes, dose changes
- Schedule parameters
  - e.g. urine testing frequency

CM developments outside BPRU for Tx of cocaine dependence

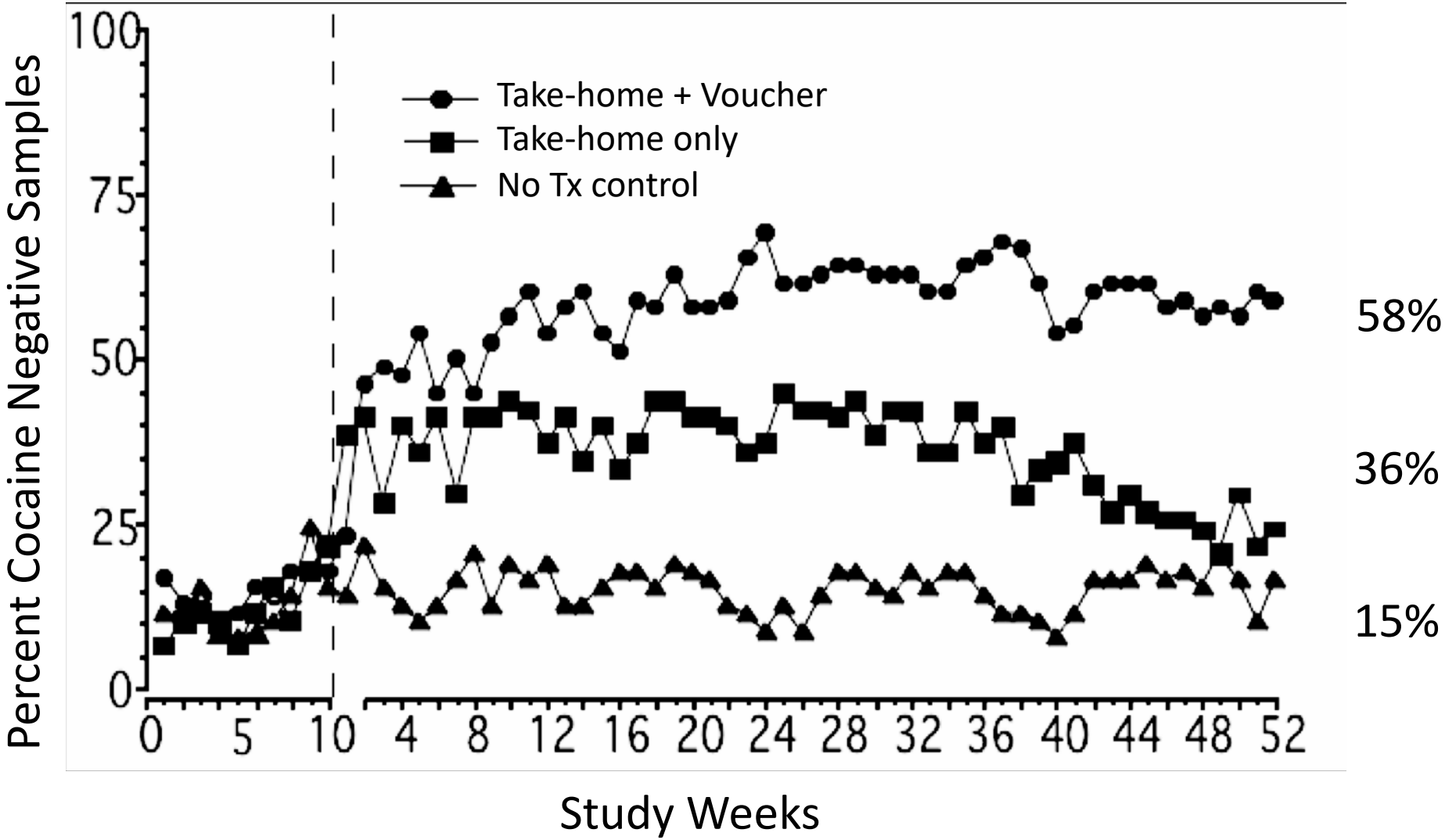
- Higgins develops voucher reinforcement
  - points with cash value used as rewards under continuous reinforcement schedule

- Petry develops “fishbowl”
  - Ticket draws with prizes awarded under an intermittent reinforcement schedule



Treating Cocaine Use in Methadone Patients

Silverman et al., 2004



CM Research at BPRU :

Innovation, Persistence
Training of future CM researchers

Steve Higgins, Ken Silverman, Warren Bickel,

Martin Iguchi, Kim Kirby, Kenzie Preston,

Michael Kidorf, Jesse Dallery, Stacy Sigmon

CTN formed to study treatment effectiveness in multiple real world settings nationwide

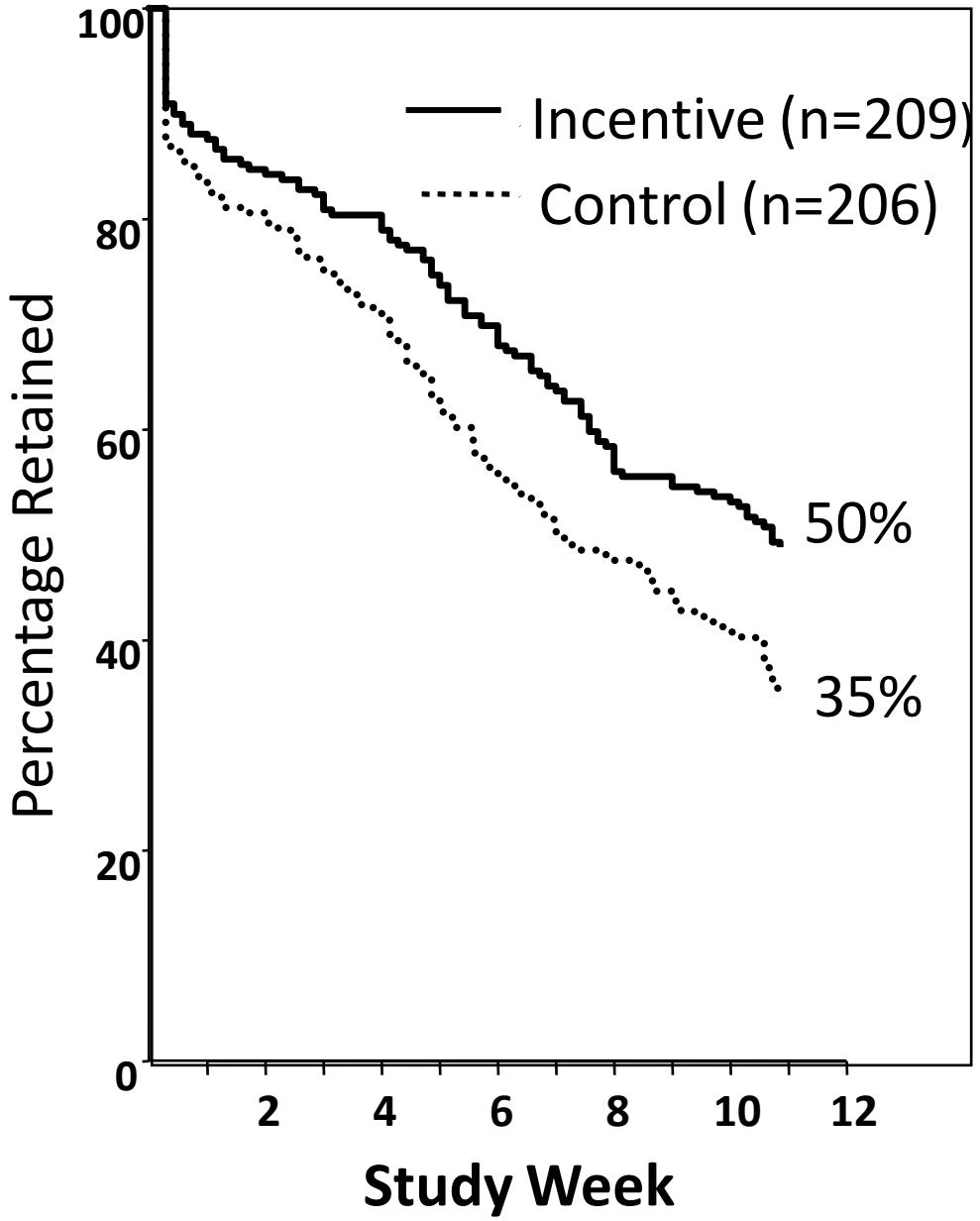
- Most early addiction treatment studies were conducted in small research clinics
- National Drug Abuse Treatment Clinical Trials Network (1999 to present) provided access to real world clinical sites and patients nationwide
- Now it was time to test research-based treatments in community clinics to bridge the gap between research and practice.

CTN 0005 & 0006
Abstinence Incentive Studies
Co-led by Stitzer and Petry

Peirce et al., 2006; Petry et al., 2005

- Large (N=800) multi-site studies conducted in community treatment programs
- Parallel studies with stimulant users in methadone maintenance clinics and with others enrolled in drug-free counseling clinics
- Target: stimulant use
- Randomized design
  - UC vs UC + prize draw incentives

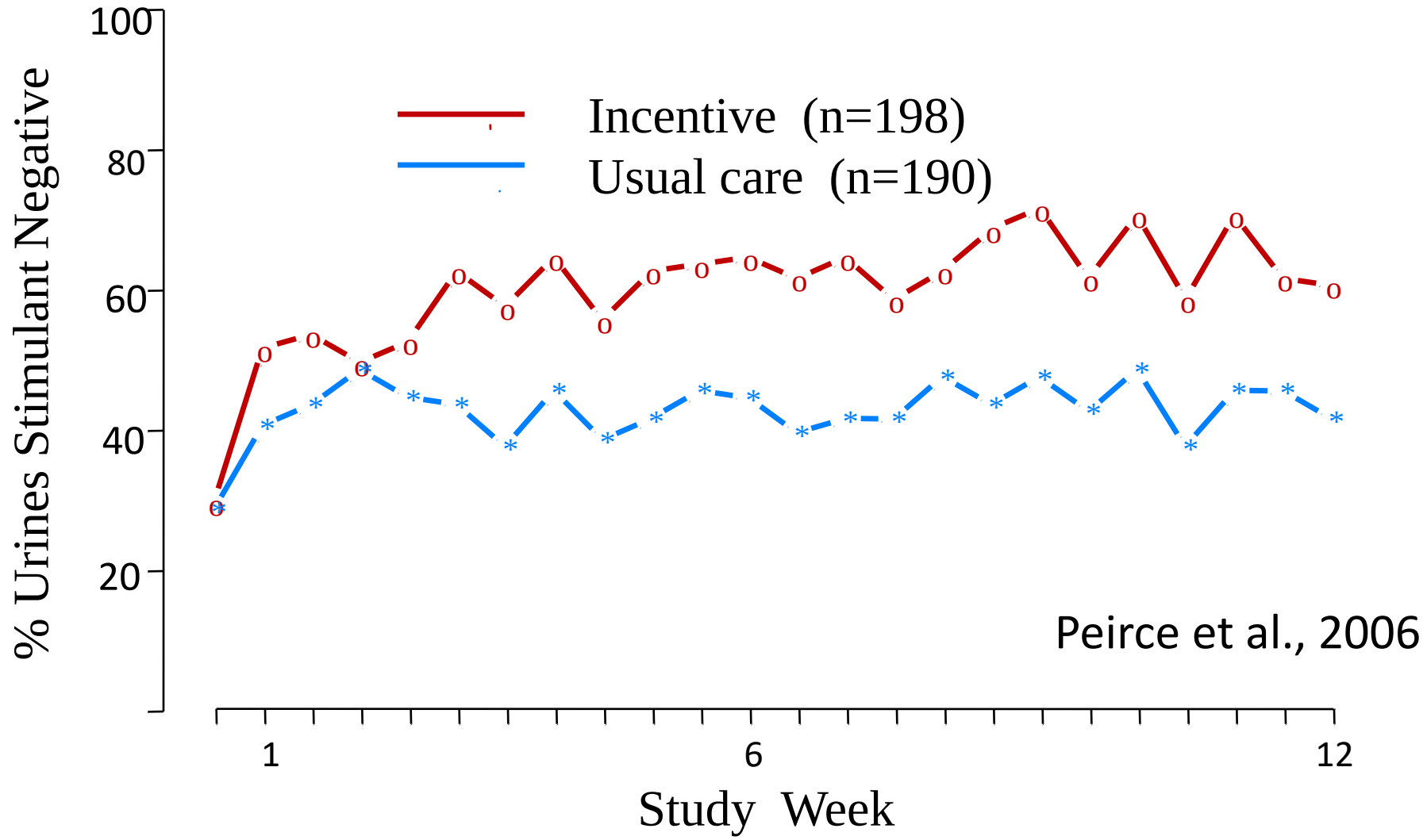
Abstinence Incentives Improved Retention in Counseling Tx



90-100% of urines submitted in both groups were stimulant-free

Petry et al., 2005

Abstinence Incentives Reduced Cocaine Use During Methadone TX

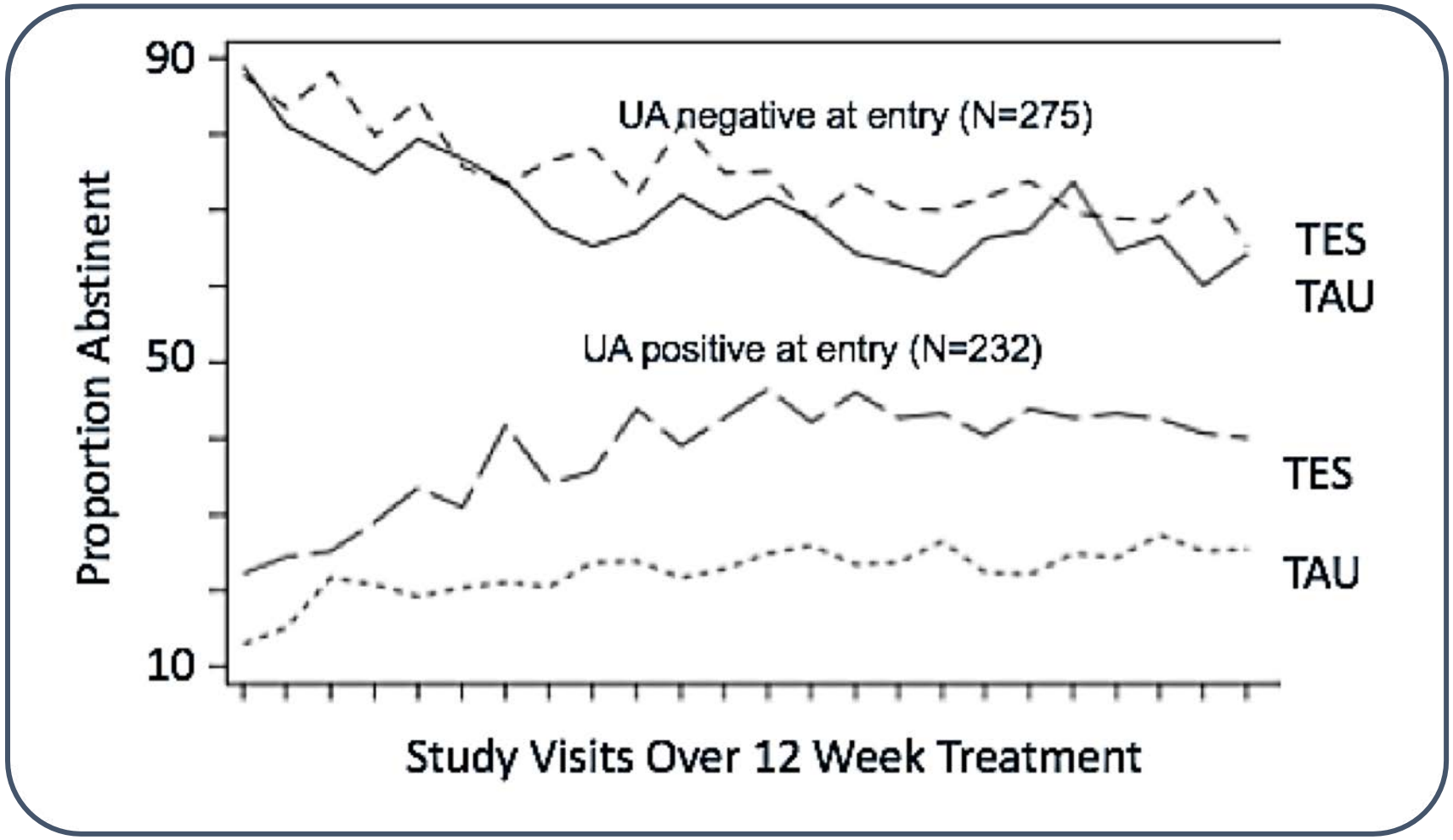


Initial CTN studies provided evidence for effectiveness of CM abstinence incentives in real world settings

More CM research in CTN: 0044 Web-based Therapeutic Education System (TES)

- Participants are all comers enrolling at community SUD counseling programs (N = 507) entering with a variety of primary drug problems
- Treatment incorporates CBT modules and abstinence incentives
  - Modules self-administered by patients
  - Urine testing conducted at clinic
  - Design is random assignment to 12 week usual care with or without TES
- Effectiveness shown for those with active drug use at treatment entry *(Campbell et al., 2014)*

CTN 0044: Web-based Treatment Therapeutic Education System (TES)



More CM research in CTN: 0049 HOPE

- HOPE study used multi-target intervention for promoting health care behaviors among HIV+ substance users (N=800)
- 3-group design: UC or Patient Navigation delivered alone (PN) or combined with contingent financial incentives (PN+CM)
- Incentives associated with substantial increases in targeted health care behaviors (medians PN+CM vs PN):
  - Navigator Visits attended: 11 vs 7
  - HIV Doctor Visits attended: 3 vs 1.5
  - Entered SUD Tx: 48% vs 26%

CM in perspective

- Addiction researchers like CM
  - Huge body of research demonstrates efficacy for every type of substance abuse, HIV medication adherence and appointment attendance

- Less widely liked/used by treatment providers in clinical practice despite status as an evidence-based practice
  - Some to do with convenience & familiarity; some to do with cost

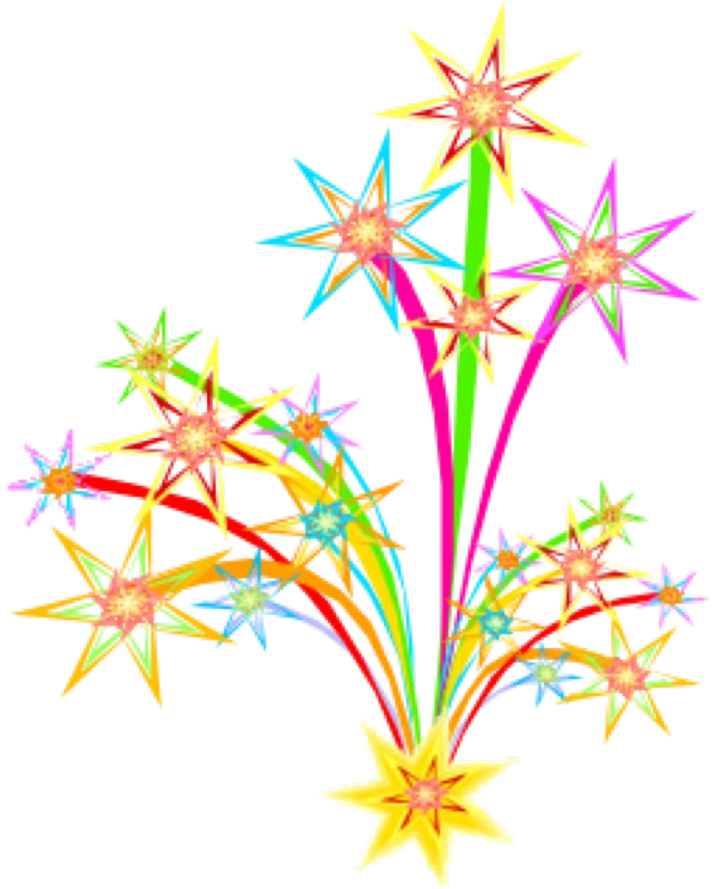
CM development update: Remote testing and phone app technology

- Remote sample testing technology has revolutionized CM delivery
  - Video home testing for carbon monoxide, alcohol, and drugs (saliva test) with reward payments download to debit cards

- Smart phone apps have been developed for convenient technology-supported delivery of CM
  - reSET deploys the web-based program (TES) tested in CTN
  - DynamiCare Rewards utilizes patient self-testing and remote delivery
  - reSET which incorporates contingent abstinence incentives has been recognized by FDA as a digital therapeutic intervention for SUD

CM well suited for 21st Century technology

- Convenience improved by remote delivery via smart phones
- Groundwork laid for expanded implementation
- Approval of a digital therapeutic may help support third party payment for CM



Contingency Management: Lingering Questions

- Is CM helpful for relapse prevention in those who stop use on their own, whether in or outside of treatment?

- How long should CM be sustained?
  - Chance of long-term abstinence directly related to duration of prior abstinence
  - Suggests individualized durations may be optimal

- How can benefits be sustained beyond the time that CM is withdrawn?
  - Role of CBT skills? Role of lifestyle change? What additional supports may be needed (e.g. peer recovery coaching)?

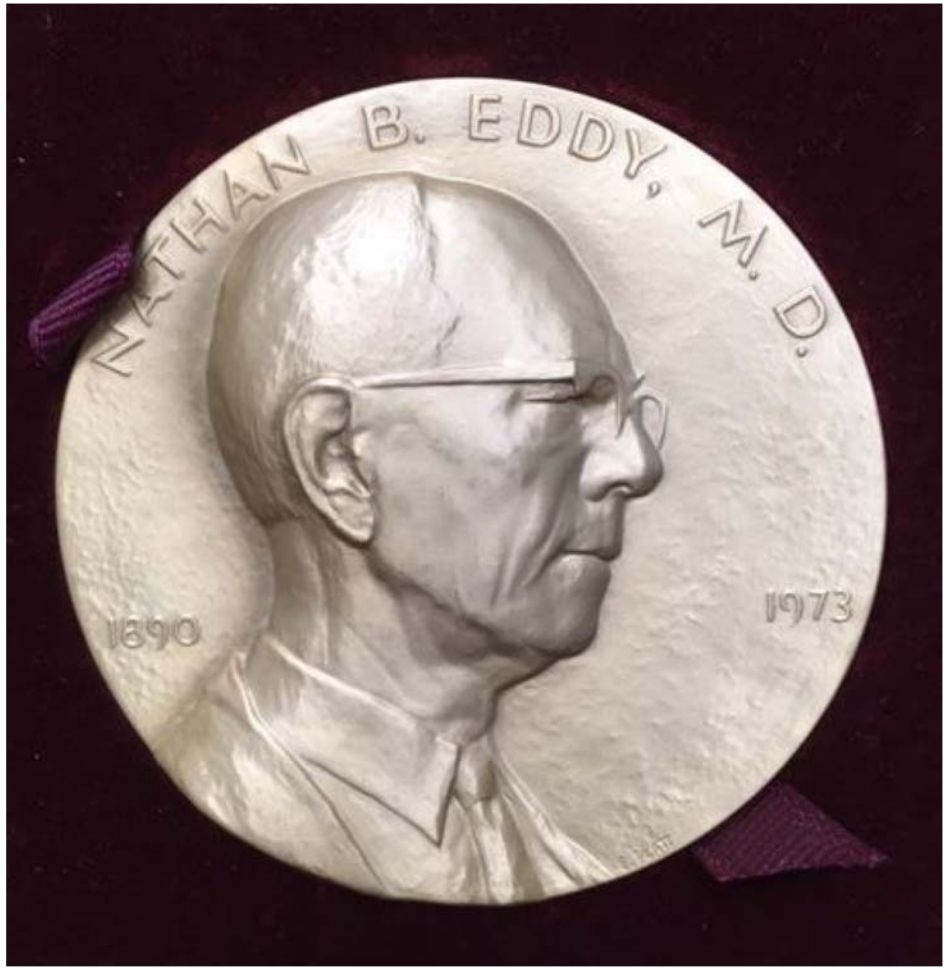
CAREER PERSPECTIVE

FROM STONE AGE TO PHONE APP AGE

Future Directions Summary

- Physical dependence development
  - Withdrawal symptoms when stopping pain medications
  - Including various meds & individual differences in sensitivity
- Medications for OUD
  - Expanded treatment capacity
  - Improved engagement and retention
- Behavior therapy
  - Efficacy/effectiveness of remote delivery methods
  - Interventions to support long-term outcomes

Nathan B. Eddy




5510 NATHAN SHOCK
DRIVE


"That's all Folks!"