

BUPRENORPHINE TREATMENT: A TRAINING FOR MULTIDISCIPLINARY ADDICTION PROFESSIONALS



NIDA/SAMHSA Blending Initiative

According to the Webster Dictionary definition

To Blend means:

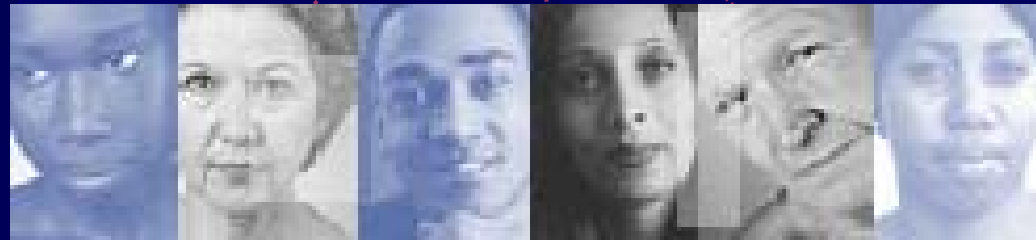
- a. combine into an integrated whole;
- b. produce a harmonious effect

<http://www.webster.com/cgi-bin/dictionary?book=Dictionary&va=blend>

NIDA/SAMHSA Blending Initiative

- Developed in 2001 by NIDA and SAMHSA/CSAT, the initiative was designed to **meld science and practice** together to improve drug abuse and addiction treatment.
- "Blending Teams," include staff from CSAT's ATTCs and NIDA researchers who develop methods for **dissemination of research results for adoption and implementation** into practice.
- With the skills, resources, and knowledge of these two Federal agencies, important **scientific findings are able to reach the frontline service providers** treating people with substance use disorders. This is **imperative to the success** of drug abuse treatment programs throughout the country.

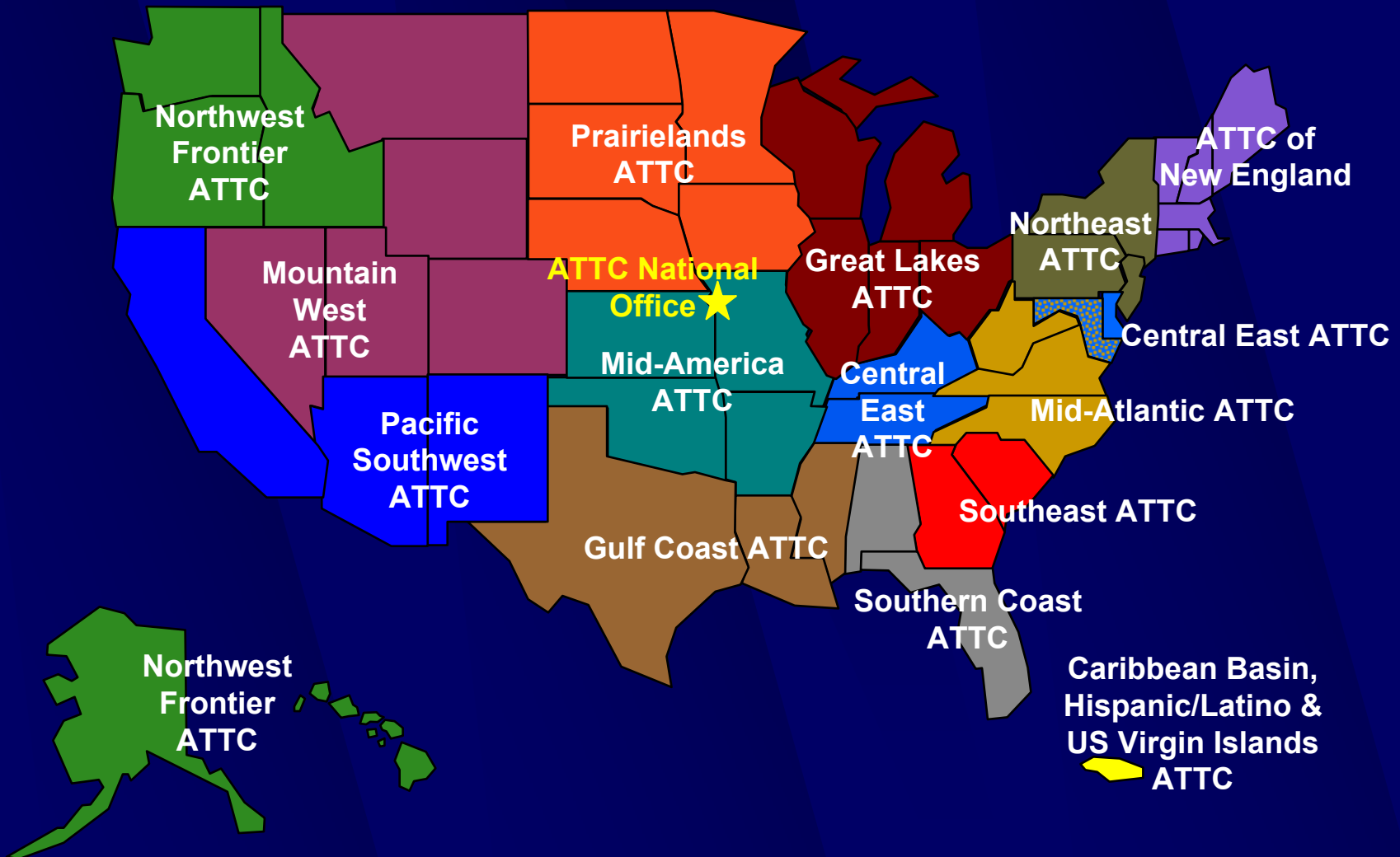
So who are the
participants in this
endeavor?





The ATTC Network

The ATTC Network

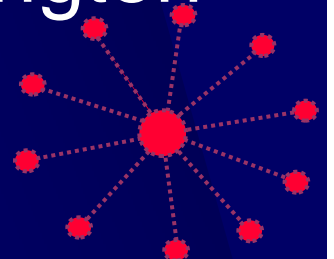




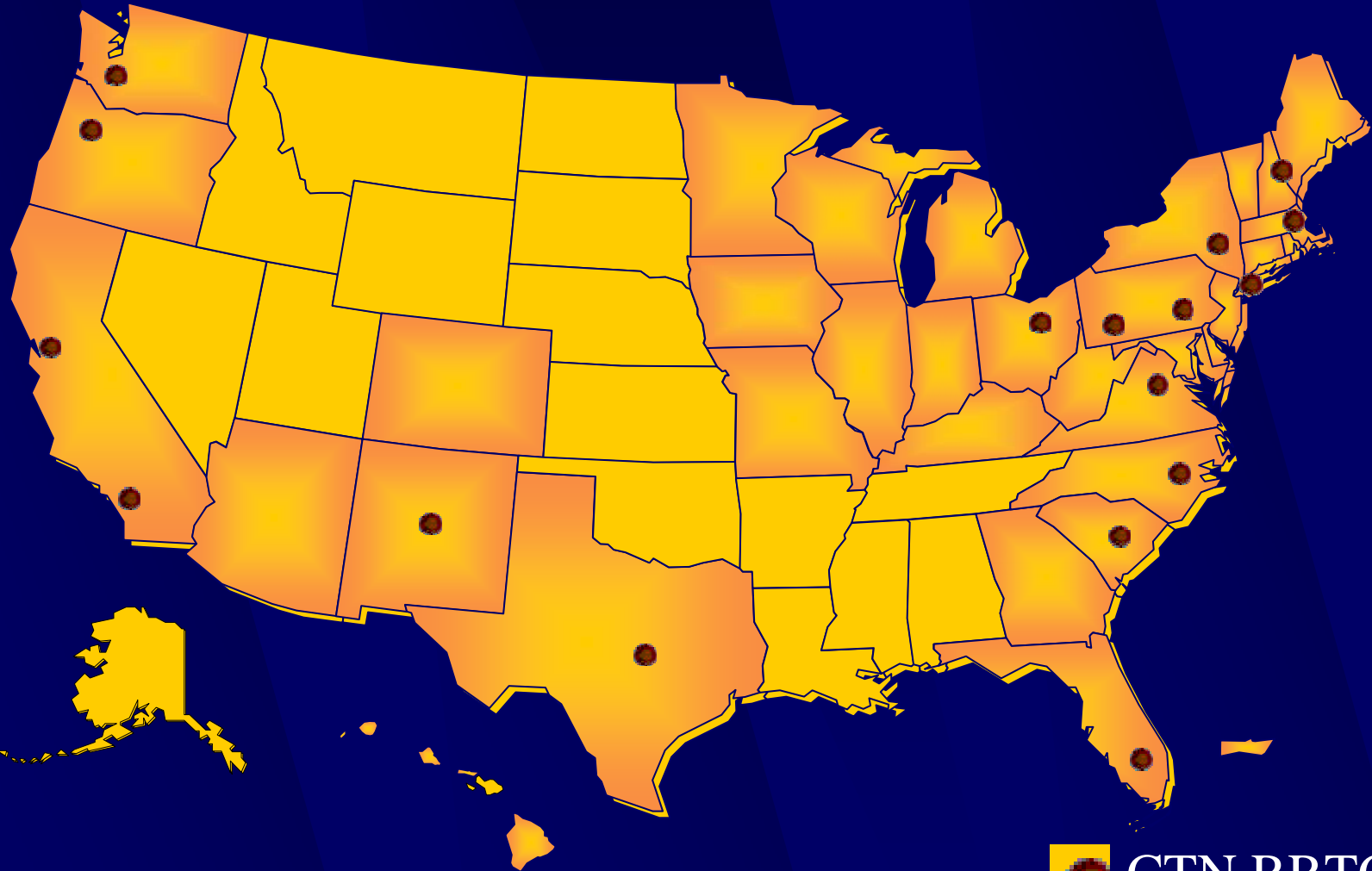
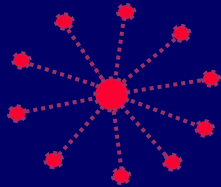
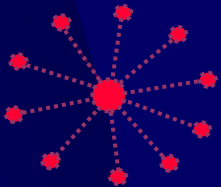
An Introduction to the Clinical Trials Network

NIDA's Clinical Trials Network

- Established in 1999
- NIDA's largest initiative to blend research and clinical practice by bringing promising therapies to community treatment providers
- Network of 17 University-based Regional Research and Training Centers (RRTCs) involving 116 Community Treatment Programs (CTPs) in 24 states, Washington D.C., and Puerto Rico



CTN Nodes



CTN RRTC



States with CTP

CTN Node



A Brief History of Opioid Treatment

BAYER

PHARMACEUTICAL PRODUCTS.

We are now sending to Physicians throughout the United States literature and samples of

ASPIRIN

The substitute for the Salicylates, agreeable of taste, free from unpleasant after-effects.

HEROIN

The Sedative for Coughs,

HEROIN HYDROCHLORIDE

Its water-soluble salt.

You will have call for them. Order a supply from your jobber.

Write for literature to

FARBENFABRIKEN OF ELBERFELD CO.

40 Stone Street, New York,

SOLE AGENTS

A Brief History of Opioid Treatment

- 1964: **Methadone** is approved.
- 1974: **Narcotic Treatment Act** limits methadone treatment to specifically licensed Opioid Treatment Programs (OTPs).
- 1984: **Naltrexone** is approved, but has continued to be rarely used (approved in 1994 for alcohol addiction).
- 1993: **LAAM** is approved (for non-pregnant patients only), but is underutilized.

A Brief History of Opioid Treatment, Continued

- 2000: Drug Addiction Treatment Act of 2000 (**DATA 2000**) expands the clinical context of medication-assisted opioid treatment.
- 2002: Tablet formulations of **buprenorphine** (Subutex[®]) and buprenorphine/naloxone (Suboxone[®]) were **approved** by the Food and Drug Administration (FDA).
- 2004: Sale and distribution of **ORLAAM[®]** is **discontinued**.

Understanding DATA 2000

Drug Addiction Treatment Act of 2000 (DATA 2000)

- Expands treatment options to include both the general health care system and opioid treatment programs.
 - Expands number of available treatment slots
 - Allows opioid treatment in office settings
 - Sets physician qualifications for prescribing the medication

DATA 2000: Physician Qualifications

Physicians must:

- Be **licensed** to practice by his/her state
- Have the **capacity to refer** patients for psychosocial treatment
- Limit their practice to 30 patients receiving buprenorphine for first year and 100 patients after that
- Be qualified to provide buprenorphine and receive a license waiver

DATA 2000: Physician Qualifications

A physician must meet one or more of the following qualifications:

- Board certified in Addiction Psychiatry
- Certified in Addiction Medicine by ASAM or AOA
- Served as Investigator in buprenorphine clinical trials
- Completed 8 hours of training by ASAM, AAAP, AMA, AOA, APA (or other organizations that may be designated by Health and Human Services)
- Training or experience as determined by state medical licensing board
- Other criteria established through regulation by Health and Human Services

Development of Subutex®/Suboxone®

- U.S. FDA approved Subutex® and Suboxone® *sublingual tablets* for opioid addiction treatment on October 8, 2002.
- Product launched in U.S. in March 2003
- Interim rule changes to federal regulation (42 CFR Part 8) on May 22, 2003 enabled Opioid Treatment Programs (specialist clinics) to offer buprenorphine.



Only physicians can prescribe the medication.

However, the entire treatment system should be engaged.



Effective treatment generally requires many facets. Treatment providers are important in helping the patients to:

- Manage physical withdrawal symptoms
- Understand the behavioral and cognitive changes resulting from drug use
- Achieve long-term changes and prevent relapse
- Establish ongoing communication between physician and community provider to ensure coordinated care
- Engage in a flexible treatment plan to help them achieve recovery

A Point of Discussion

Dependence vs. Addiction:
What's the Difference?

Possible Acute Effects of Opioid Use

- Surge of pleasurable sensation = “rush”
- Warm flushing of skin
- Dry mouth
- Heavy feeling in extremities
- Drowsiness
- Clouding of mental function
- Slowing of heart rate and breathing
- Nausea, vomiting, and severe itching

Consequences of Opioid Use

- Addiction
- Overdose
- Death
- Use related (e.g., HIV infection, malnutrition)
- Negative consequences from injection:
 - Infectious diseases (e.g., HIV/AIDS, Hepatitis B and C)
 - Collapsed veins
 - Bacterial infections
 - Abscesses
 - Infection of heart lining and valves
 - Arthritis and other rheumatologic problems

Opioid Withdrawal Syndrome

Acute Symptoms

- Pupillary dilation
- Lacrimation (watery eyes)
- Rhinorrhea (runny nose)
- Muscle spasms (“kicking”)
- Yawning, sweating, chills, gooseflesh
- Stomach cramps, diarrhea, vomiting
- Restlessness, anxiety, irritability

Opioid Withdrawal Syndrome

Protracted Symptoms

- Deep muscle aches and pains
- Insomnia, disturbed sleep
- Poor appetite
- Reduced libido, impotence, anorgasmia
- Depressed mood, anhedonia
- Drug craving and obsession

Development of Tablet Formulations of Buprenorphine

- Buprenorphine is marketed for opioid treatment under the trade names of Subutex® (buprenorphine) and Suboxone® (buprenorphine/naloxone)
- Over 25 years of research
- Over 5,000 patients exposed during clinical trials
- Proven safe and effective for the treatment of opioid addiction

Buprenorphine: A Science-Based Treatment

Clinical trials have established the effectiveness of buprenorphine for the treatment of heroin addiction. Effectiveness of buprenorphine has been compared to:

- Placebo (Johnson et al. 1995; Ling et al. 1998; Kakko et al. 2003)
- Methadone (Johnson et al. 1992; Strain et al. 1994a, 1994b; Ling et al. 1996; Schottenfield et al. 1997; Fischer et al. 1999)
- Methadone and LAAM (Johnson et al. 2000)

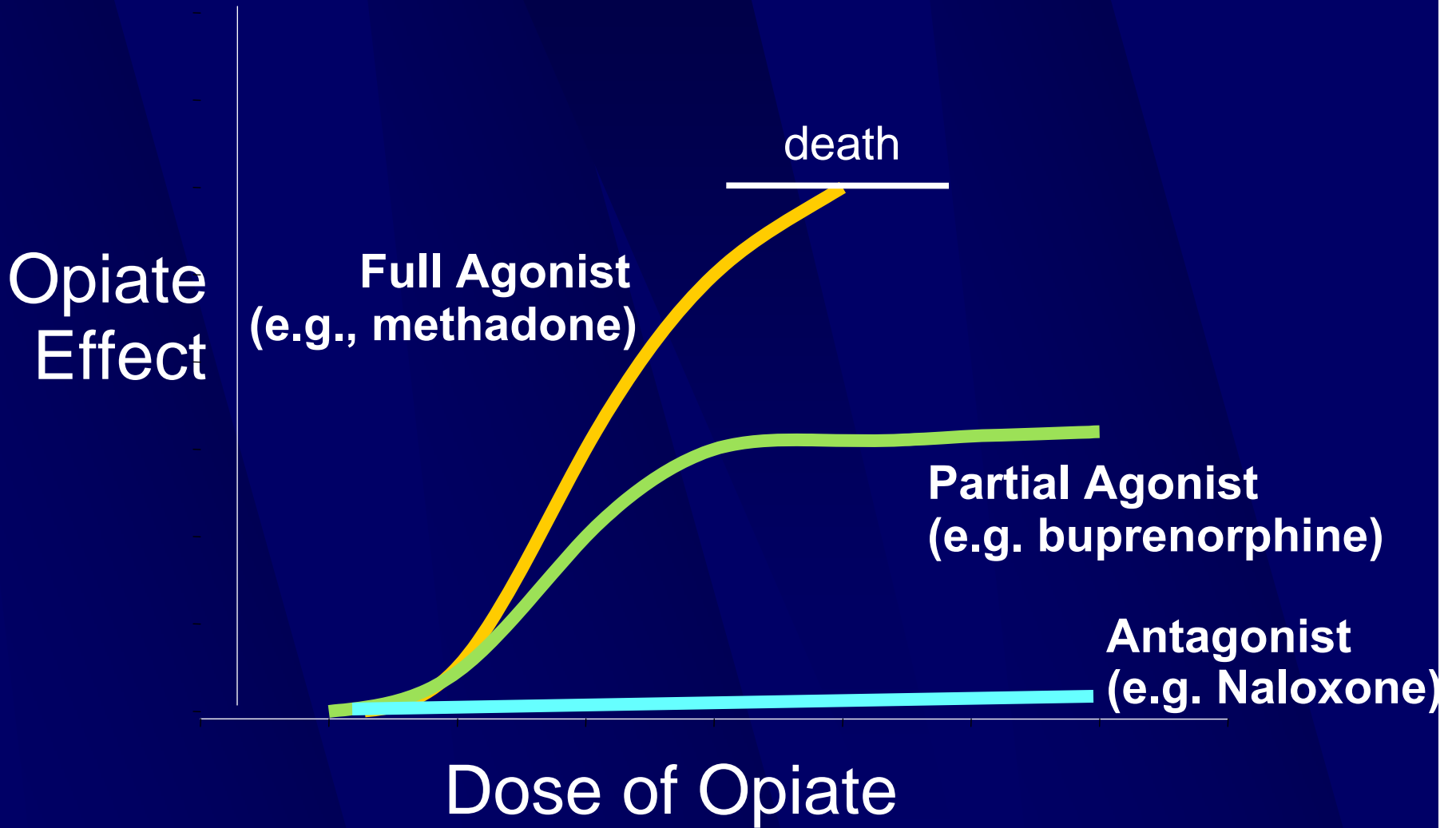
Buprenorphine Research Outcomes

- Buprenorphine is as effective as moderate doses of methadone.
- Buprenorphine is as effective as moderate doses of LAAM.
- Buprenorphine's partial agonist effects make it mildly reinforcing, encouraging medication compliance.
- After a year of buprenorphine plus counseling, 75% of patients retained in treatment compared to 0% in a placebo-plus-counseling condition.

The Role of Buprenorphine in Opioid Treatment

- Partial Opioid Agonist
 - Produces a ceiling effect at higher doses
 - Has effects of typical opioid agonists—these effects are dose dependent up to a limit
 - Binds strongly to opiate receptor and is long-acting
- Safe and effective therapy for opioid maintenance and detoxification

Partial vs. Full Opioid Agonist

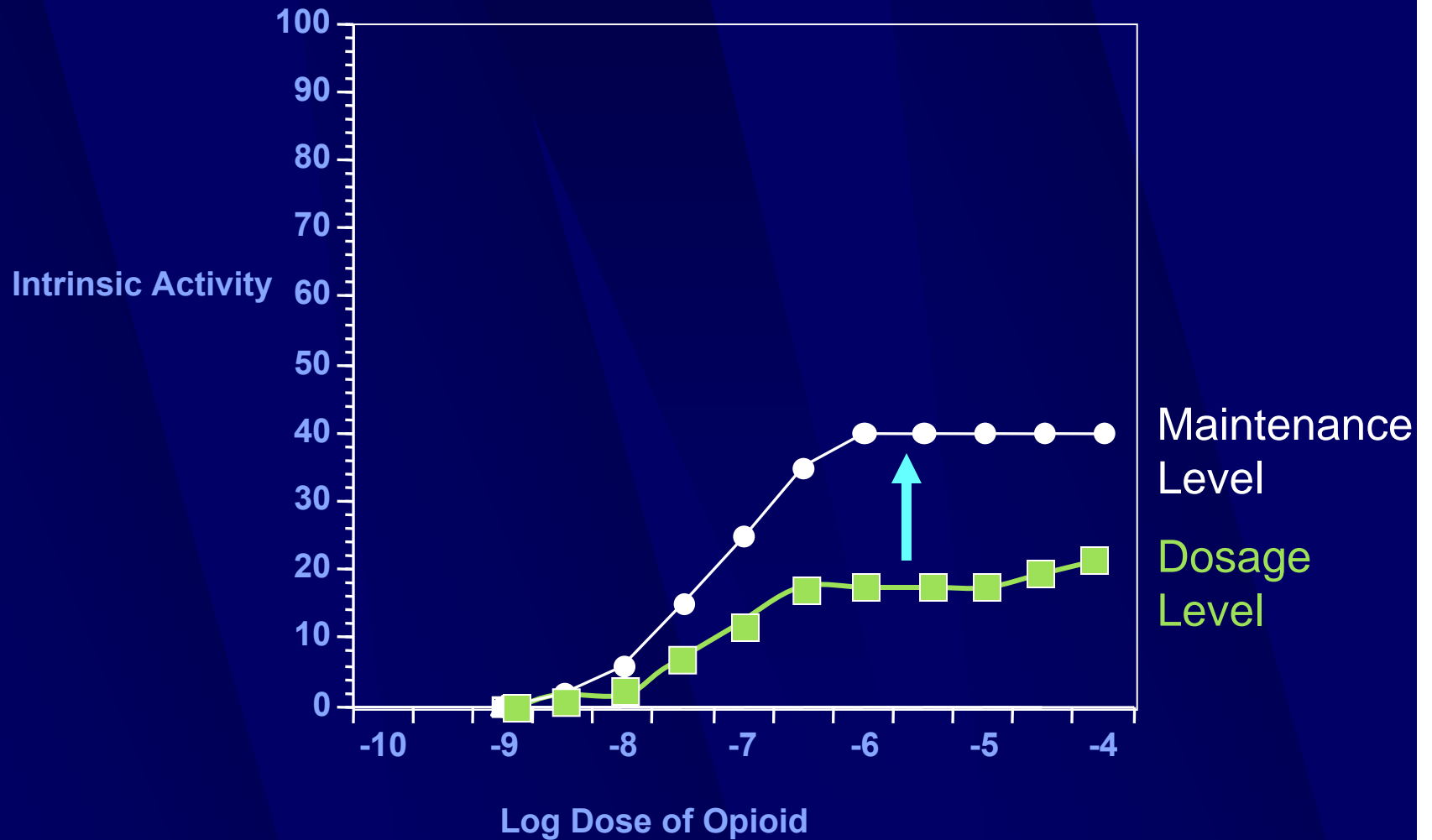


Transferring Patients Onto Buprenorphine: 3 Ways Significant Withdrawal Could Occur

Dose too low?

Insufficient
agonist
effects

If dose is too low, the patient will experience withdrawal



Transferring Patients Onto Buprenorphine: 3 Ways Significant Withdrawal Could Occur

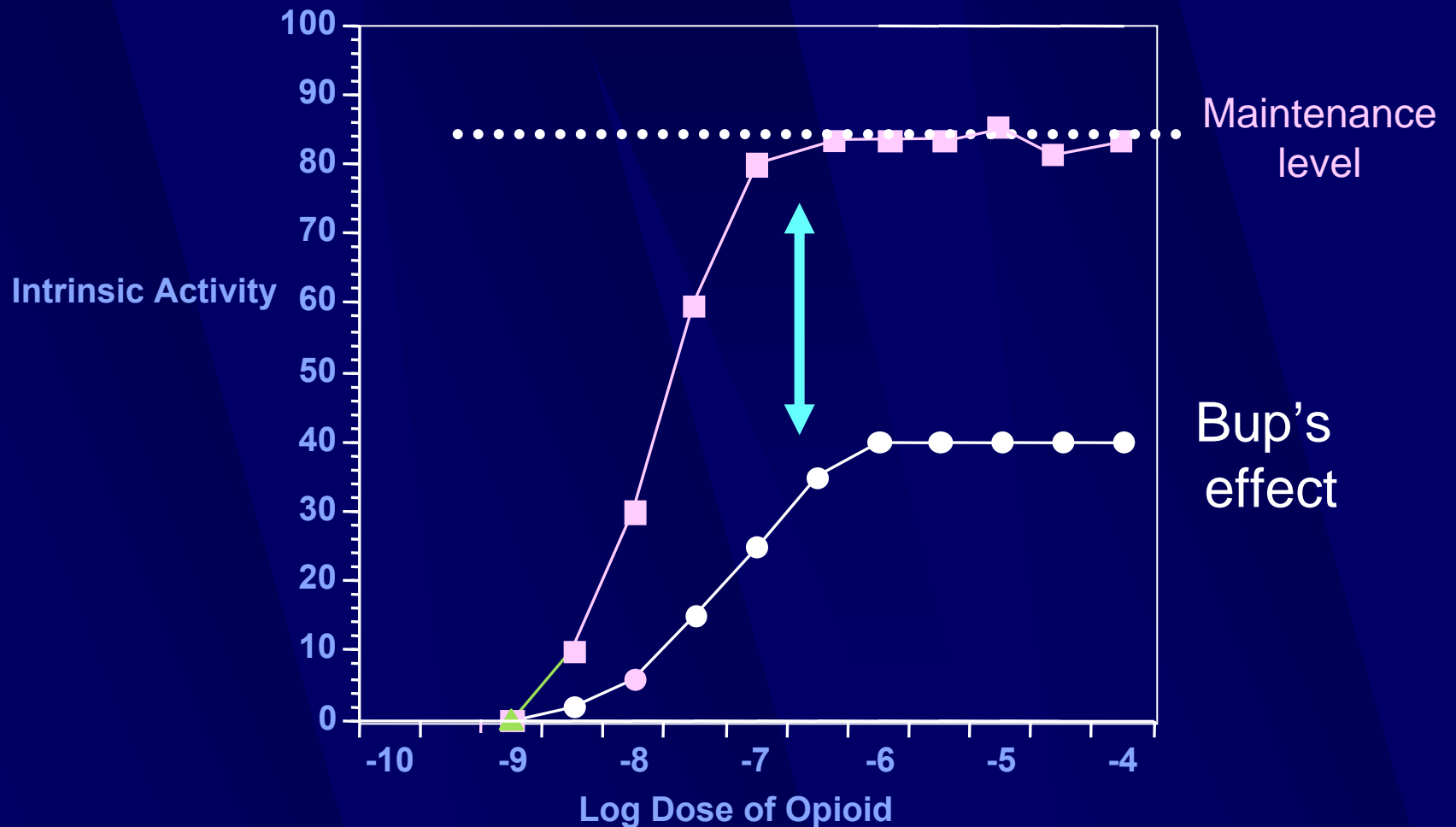
Dose too low?

Insufficient
agonist
effects

Not full agonist

May not
fully
substitute

If the patient needs a high level of medication to achieve maintenance, the ceiling effect of buprenorphine may result in withdrawal



Transferring Patients Onto Buprenorphine: 3 Ways Significant Withdrawal Could Occur

Dose too low?

Insufficient
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effects

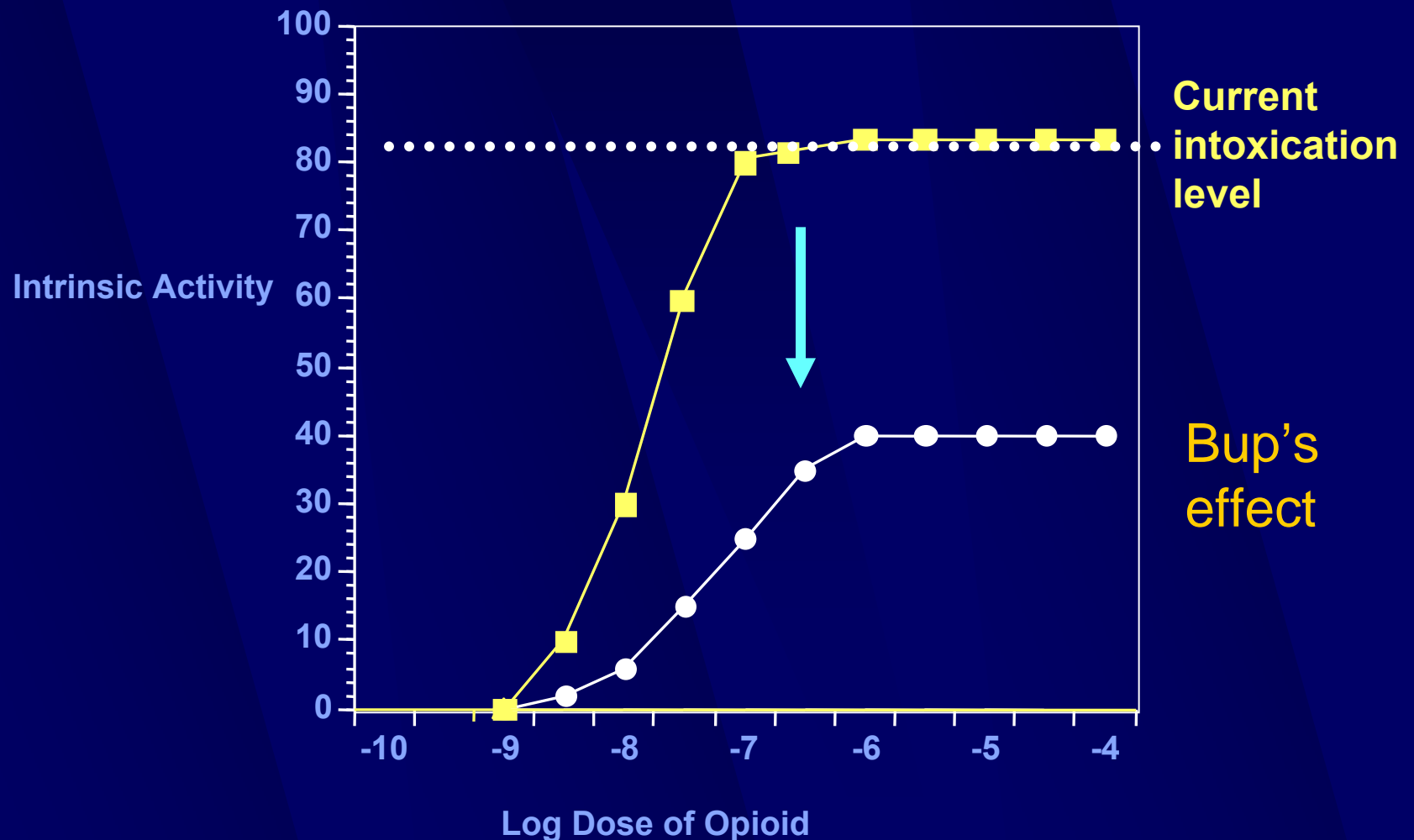
Not full agonist

May not
fully
substitute

Precipitates
Withdrawal

Ceiling
effect

Buprenorphine will replace other opioids at the receptor site. The patient therefore experiences withdrawal



Advantages of Buprenorphine in the Treatment of Opioid Addiction

1. Patient can participate fully in treatment activities and other activities of daily living easing their transition into the treatment environment
2. Limited potential for overdose
3. Minimal subjective effects (e.g., sedation) following a dose
4. Available for use in an office setting
5. Lower level of physical dependence

Advantages of Buprenorphine/Naloxone in the Treatment of Opioid Addiction

- Combination tablet is being marketed for U.S. use
- 6. Discourages IV use
- 7. Diminishes diversion
- 8. Allows for take-home dosing

Disadvantages of Buprenorphine in the Treatment of Opioid Addiction

1. Greater medication cost
2. Lower level of physical dependence (i.e., patients can discontinue treatment)
3. Not detectable in most urine toxicology screenings

Why was Buprenorphine/Naloxone Combination Developed?

- Developed in response to increased reports of buprenorphine abuse outside of the U.S.
- The combination tablet is specifically designed to decrease buprenorphine abuse by injection, especially by out of treatment opioid users.

What is the Ratio of Buprenorphine to Naloxone in the Combination Tablet?

- Each tablet contains buprenorphine and naloxone in a 4:1 ratio
 - Each 8 mg tablet contains 2 mg of naloxone
 - Each 2 mg tablet contains 0.5 mg of naloxone
- Ratio was deemed optimal in clinical studies
 - Preserves buprenorphine's therapeutic effects when taken as intended sublingually
 - Sufficient dysphoric effects occur if injected by some physically dependent persons to discourage abuse.

Why Combining Buprenorphine and Naloxone Sublingually Works

- Buprenorphine and naloxone have different sublingual (SL) to injection potency profiles that are optimal for use in a combination product.

SL Bioavailability

Buprenorphine 40-60%

Naloxone 10% or less

Injection to Sublingual Potency

Buprenorphine \approx 2:1

Naloxone \approx 15:1

Buprenorphine/Naloxone: What You Need to know

- Basic pharmacology, pharmacokinetics, and efficacy is the *same* as buprenorphine alone.
- Partial opioid agonist; ceiling effect at higher doses
- Blocks effects of other agonists
- Binds strongly to opioid receptor, long acting

The Use of Buprenorphine in the Treatment of Opioid Addiction

Induction

Maintenance

**Tapering Off/Medically-Assisted
Withdrawal**

Induction

Induction Phase

Working to establish the appropriate dose of medication for patient to discontinue use of opiates with minimal withdrawal symptoms, side-effects, and craving



Buprenorphine is administered sublingually.

**What will the tablets look like?
How will they taste?**

Light orange tablet

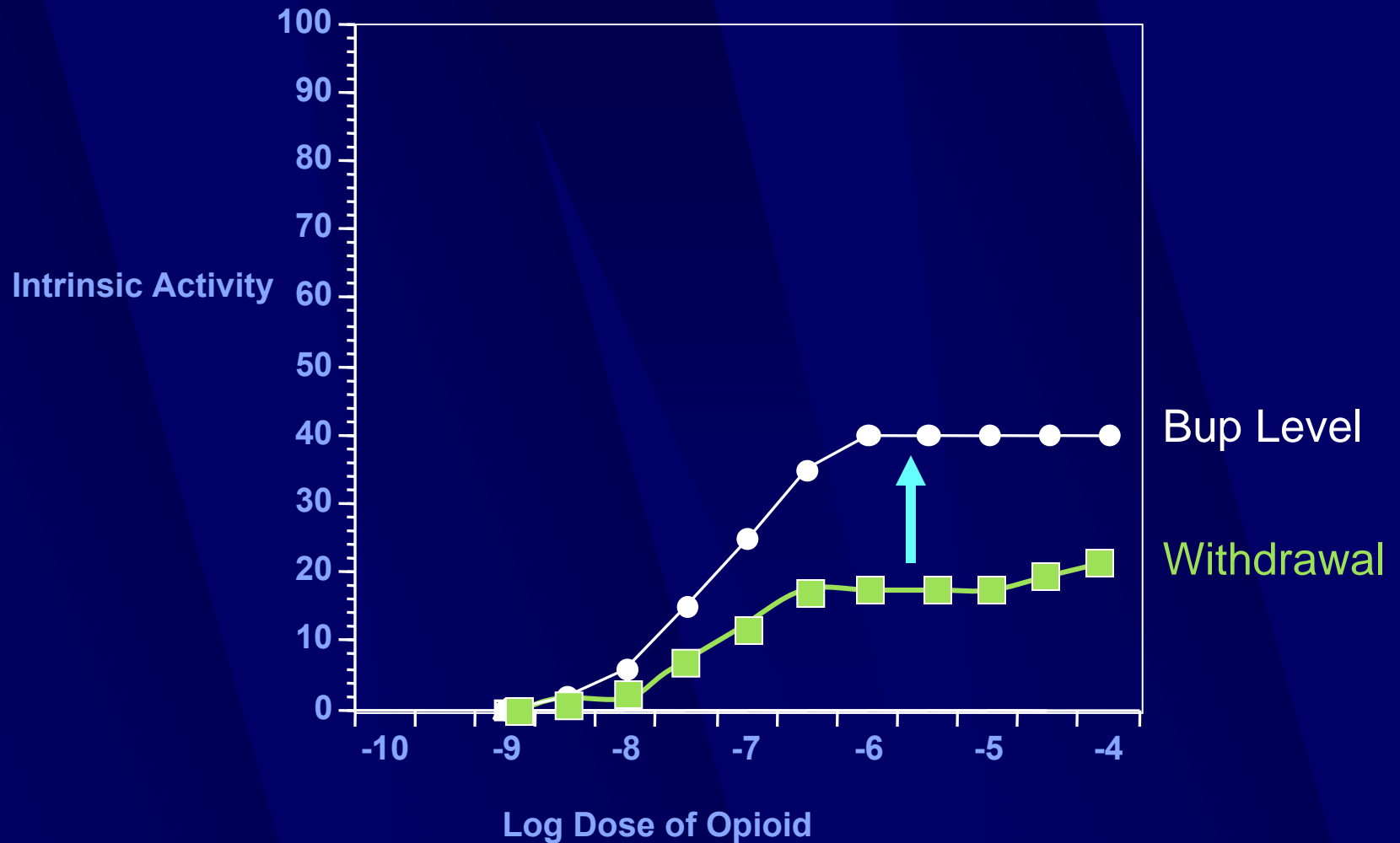
Flavor = natural lemon & lime

Sweetener = acesulfame potassium



This is done to overcome the perceived bitterness of the naloxone hydrochloride in the Suboxone tablets. The orange color has been added to ensure clear differentiation between Subutex and Suboxone tablets.

If the patient is in mild withdrawal the medicine will bring them back to a comfortable level



Direct Buprenorphine Induction from Short-Acting Opioids

- Ask patient to abstain from short-acting opioid (e.g., heroin) for at least 6 hrs. and be in mild withdrawal before administering buprenorphine/naloxone.
- When transferring from a short-acting opioid, be sure the patient provides a methadone-negative urine screen before 1st buprenorphine dose.

Direct Buprenorphine Induction from Long-Acting Opioids

- Controlled trials are needed to determine optimal procedures for inducing these patients.
- Data is also needed to determine whether the buprenorphine only or the buprenorphine/naloxone tablet is optimal when inducing these patients.

Direct Buprenorphine Induction from Long-Acting Opioids

- Clinical experience has suggest that induction procedures with patients receiving long-acting opioids (e.g. methadone-maintenance patients) are basically the same as those used with patients taking short-acting opioids, except:
 - The time interval between the last dose of medication and the first dose of buprenorphine must be **increased**.
 - **At least 24 hrs should elapse** before starting buprenorphine and longer time periods may be needed (up to 48 hrs).
 - Urine drug screening should indicate no other illicit opiate use at the time of induction.

Stabilization and Maintenance

Stabilization Phase

Patient experiences no withdrawal symptoms, side-effects, or craving

Maintenance Phase

Goals of Maintenance Phase:

Help the person stop and stay away from illicit drug use and problematic use of alcohol

1. Continue to monitor cravings to prevent relapse
2. Address psychosocial and family issues

Maintenance Phase

Psychosocial and family issues to be addressed:

- a) Psychiatric comorbidity
- b) Family and support issues
- c) Time management
- d) Employment/financial issues
- e) Pro-social activities
- f) Legal issues
- g) Secondary drug/alcohol use

Medically-Assisted Withdrawal

(a.k.a. Dose Tapering)

Buprenorphine Withdrawal

- Working to provide a smooth transition from a physically-dependent to non-dependent state, with medical supervision
- Medically supervised withdrawal (detoxification) is accompanied with and followed by psychosocial treatment, and sometimes medication treatment (i.e., naltrexone) to minimize risk of relapse.

Medically-Assisted Withdrawal (Detoxification)

- Outpatient and inpatient withdrawal are both possible
- How is it done?
 - Switch to longer-acting opioid (e.g., buprenorphine)
 - Taper off over a period of time (a few days to weeks depending upon the program)
 - Use other medications to treat withdrawal symptoms
 - Use clonidine and other non-narcotic medications to manage symptoms during withdrawal

The Two Buprenorphine-Naloxone Protocols

NIDA-CTN 0001:

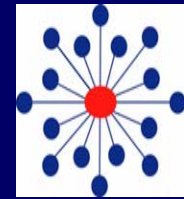
**Buprenorphine-Naloxone vs. Clonidine for Short-Term
Inpatient Opiate Detoxification**

NIDA-CTN 0002:

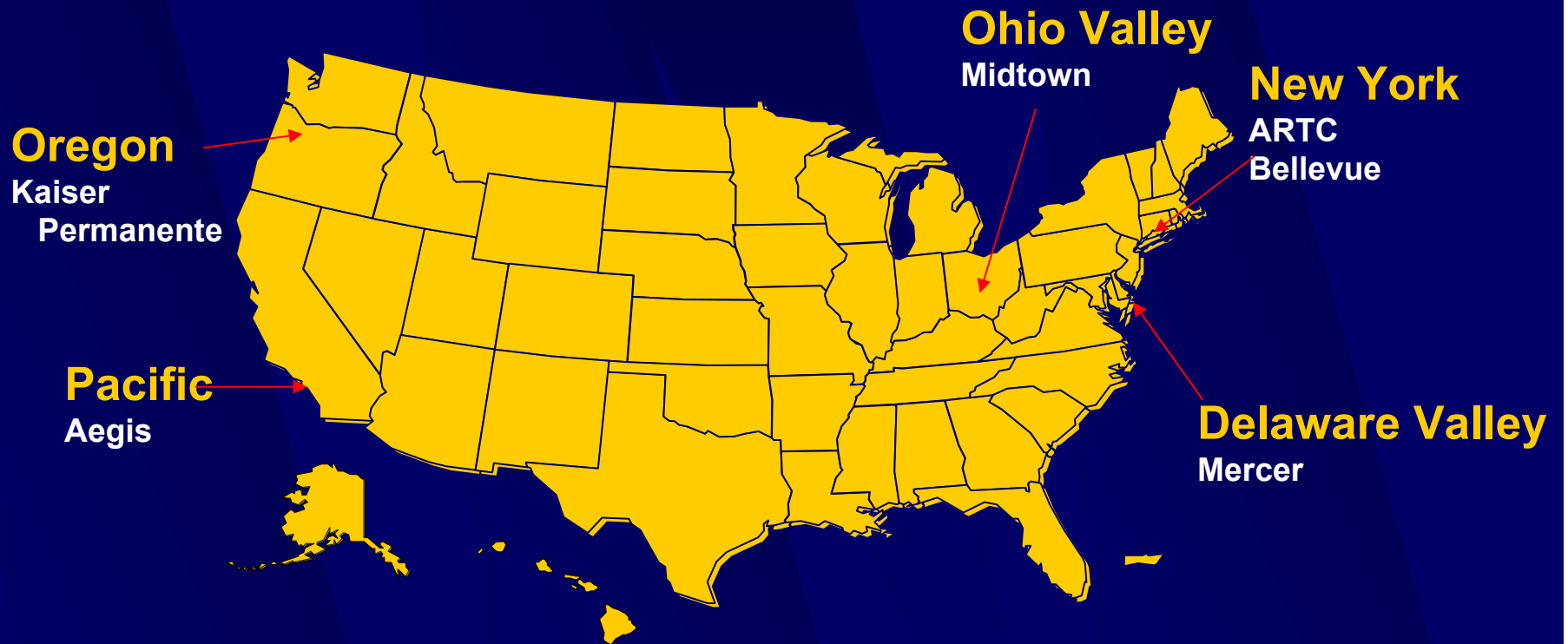
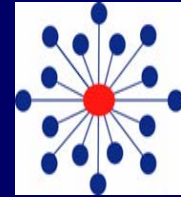
**Buprenorphine-Naloxone vs. Clonidine for Short-Term
Outpatient Opiate Detoxification**

**Initiated in 8 Regional Nodes and
12 Community Treatment Programs**

Site Participation: NIDA-CTN 0001



Site Participation: NIDA-CTN 0002



NIDA CTN 001/002 Buprenorphine-Naloxone Detoxification Protocols

- Two, open-label, randomized clinical trials
- Compared Buprenorphine-Naloxone (BUP/NX) and Clonidine for Short-Term (2 weeks) opioid Detoxification in Residential or Outpatient Settings

Community Treatment Programs

6 Inpatient

- 2 Therapeutic Communities
- 1 Free-standing, Chemical Dependency Hospital
- 2 Detox Units with Integrated Addiction and Mental Health Services
- 1 Long Term Residential

Usual care approaches:
50% methadone, 50%
clonidine

6 Outpatient

- 4 Opioid Treatment Programs
- 1 HMO
- 1 Community Mental Health Center

Usual care approaches:
methadone in OTPs and
clonidine in HMO

Study Schema

1. Obtain Informed Consent
2. Perform Screening/Baseline Assessments

Randomize (2:1) and Enroll

N=240
Buprenorphine/Naloxone
13 days detoxification

N=120
Clonidine
13 days detoxification

Follow-up at 1 month

Follow-up at 3 months

Follow-up at 6 months

Primary Efficacy Endpoint

- It is hypothesized that BUP/NX detoxification, compared to clonidine, will be associated with a better treatment response.
- A treatment responder = anyone who completes the 13-day detoxification and whose last urine specimen is negative for opioids.

So,

what did we find?



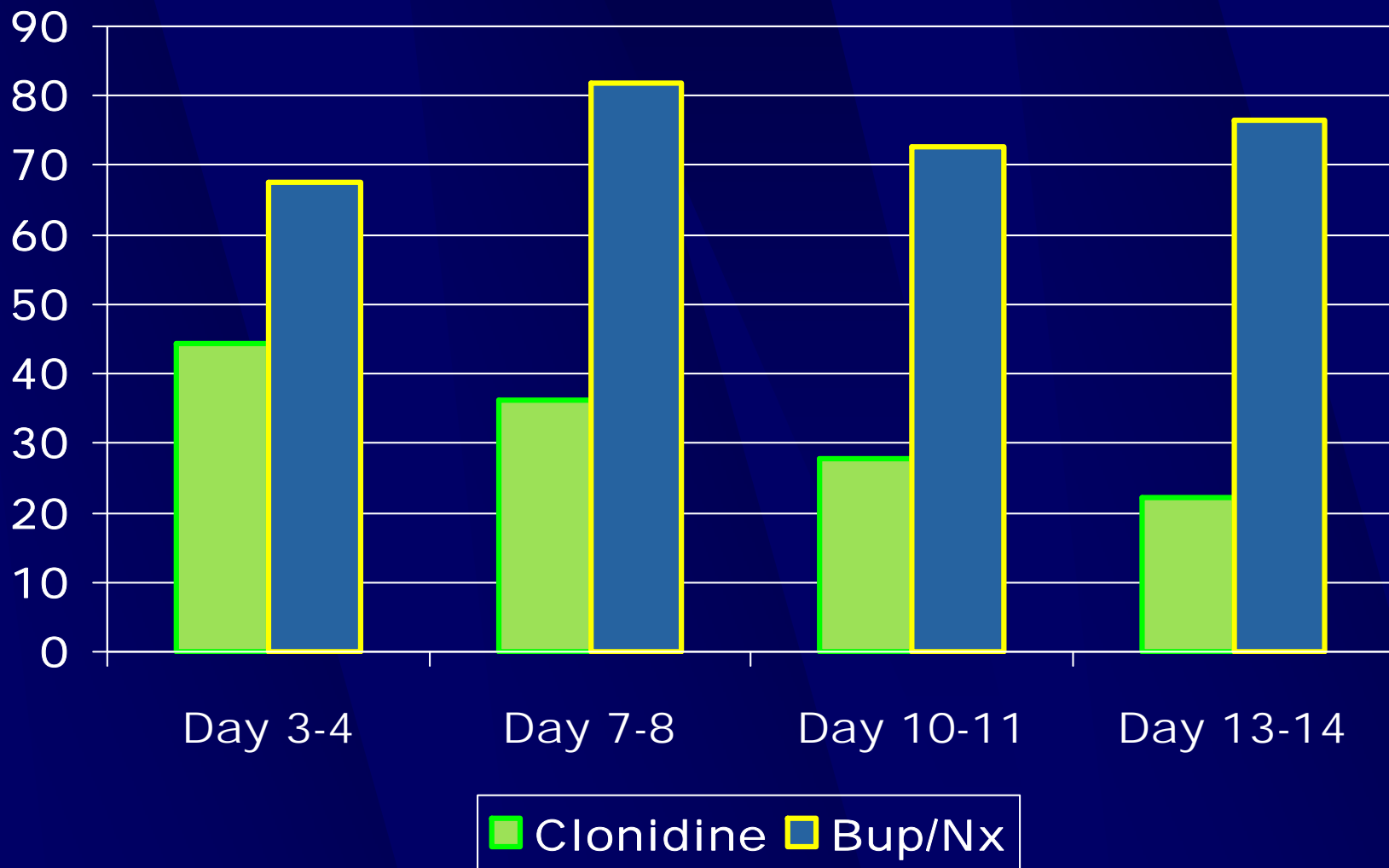
Demographics 0001 (Inpatient)

	Bup/Nx	Clonidine	Total
Sex No. (%)			
Male	61	58	60
Female	39	42	40
Race No. (%)			
White	56	56	56
Black	19	19	19
Hispanic	12	17	16
Other	9	8	9
Age in Years: Mean (Range 21-61)	35.6	37.4	-
Employed (%)	-	-	66
Mean Education in Years (SD)	-	-	12.8 (1.7)
Mean Years of Heroin Use (SD)	-	-	6.6 (8.1)

Present and Opioid Negative 0001 (Inpatient)

Present and opioid neg	Bup/Nx (N)	%	Clonidine (N)	%
N	77		36	
Day 3 or 4	52	67.5	16	44.4
Day 7 or 8	63	81.8	13	36.1
Day 10 or 11	56	72.7	10	27.8
Day 13 or 14	59	76.6	8	22.2

Present and Opioid Negative 0001 (Inpatient)



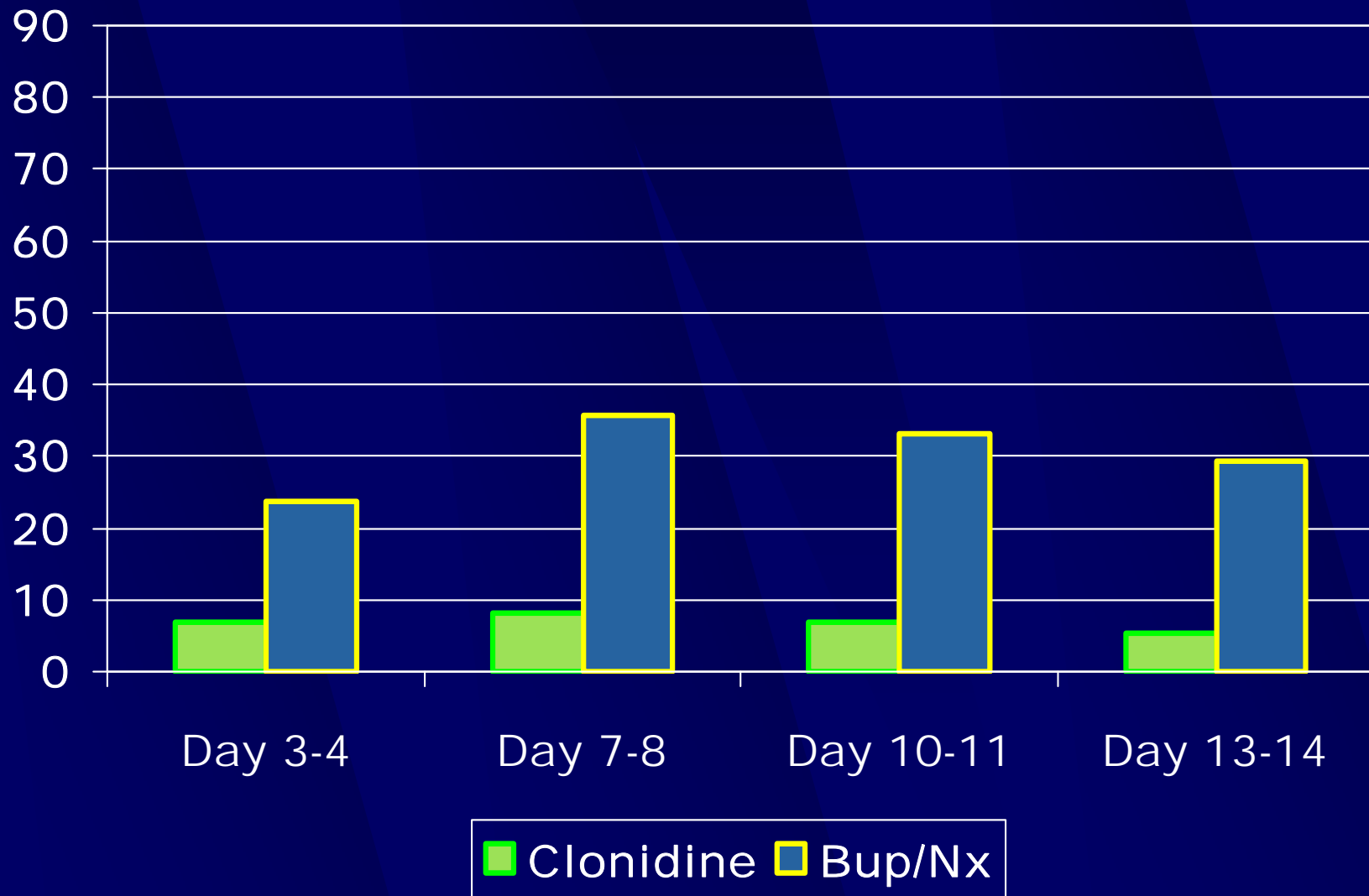
Demographics 0002 (Outpatient)

	Bup/Nx	Clonidine	Total
Sex No. (%)			
Male	73	69	72
Female	27	31	28
Race No. (%)			
White	40	40	40
Black	36	28	37
Hispanic	21	13	20
Other	3	3	3
Age in Years: Mean (Range 21-61)	38.3	40.0	-
Employed (%)	-	-	56.8
Mean Education in Years (SD)	-	-	12.4 (2.1)
Mean Years of Heroin Use (SD)	-	-	9.4 (9.6)

Present and Opioid Negative 0002 (Outpatient)

Present and opioid neg	Bup/Nx (N)	%	Clonidine (N)	%
N	157		74	
Day 3 or 4	37	23.6	5	6.8
Day 7 or 8	56	35.7	6	8.1
Day 10 or 11	52	33.1	5	6.8
Day 13 or 14	46	29.3	4	5.4

Present and Opioid Negative 0002 (Outpatient)



NNT: Number Needed to Treat

CTN 0001 (Inpatient)

- NNT for Bup/Nx $77/59 = 1.31$
- NNT for Clonidine $36/8 = 4.5$

NNT Clonidine : BupNx = 3.44

CTN 0002 (Outpatient)

- NNT for Bup/Nx: $157/46 = 3.4$
- NNT for Clonidine: $74/4 = 18.5$

NNT Clonidine : Bup/Nx = 5.44

*NNT= Number of patients needed to treat
to achieve 1 treatment success*