BUPRENORPHINE TREATMENT: A TRAINING FOR MULTIDISCIPLINARY ADDICTION PROFESSIONALS
According to the Webster Dictionary definition

To **Blend** means:

a. combine into an integrated whole;

b. produce a harmonious effect

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
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
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,
Selling 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.

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

- 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
Developed 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
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**

<table>
<thead>
<tr>
<th>Opiate Effect</th>
<th>Dose of Opiate</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Full Agonist</strong> (e.g., methadone)</td>
<td>death</td>
</tr>
<tr>
<td><strong>Partial Agonist</strong> (e.g., buprenorphine)</td>
<td></td>
</tr>
<tr>
<td><strong>Antagonist</strong> (e.g., Naloxone)</td>
<td></td>
</tr>
</tbody>
</table>
Transferring Patients Onto Buprenorphine: 3 Ways Significant Withdrawal Could Occur
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 agonist 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.

Intrinsic Activity

Log Dose of Opioid

Current intoxication level

Bup’s effect
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

1. Combination tablet is being marketed for U.S. use
2. Discourages IV use
3. Diminishes diversion
4. 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.

<table>
<thead>
<tr>
<th>SL Bioavailability</th>
<th>Injection to Sublingual Potency</th>
</tr>
</thead>
<tbody>
<tr>
<td>Buprenorphine 40-60%</td>
<td>Buprenorphine ≈ 2:1</td>
</tr>
<tr>
<td>Naloxone 10% or less</td>
<td>Naloxone ≈ 15:1</td>
</tr>
</tbody>
</table>

SOURCE: Amass et al., 2004.
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 = acesulfam 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 inducting these patients.
- Data is also needed to determine whether the buprenorphine only or the buprenorphine/naloxone tablet is optimal when inducting 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

Pacific
Betty Ford Center

Great Lakes
Shar House

Ohio Valley
Maryhaven

Long Island
Phoenix House

Florida
Operation PAR
Center for DFL
Site Participation: NIDA-CTN 0002

- Pacific
  - Kaiser Permanente
- Oregon
  - Kaiser Permanente
- Delaware Valley
  - Mercer
- New York
  - ARTC
  - Bellevue
- Ohio Valley
  - Midtown
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
<table>
<thead>
<tr>
<th>Inpatient</th>
<th>Outpatient</th>
</tr>
</thead>
<tbody>
<tr>
<td>2 Therapeutic Communities</td>
<td>4 Opioid Treatment Programs</td>
</tr>
<tr>
<td>1 Free-standing, Chemical</td>
<td>1 HMO</td>
</tr>
<tr>
<td>Dependency Hospital</td>
<td>1 Community Mental Health</td>
</tr>
<tr>
<td>2 Detox Units with Integrated Addiction and Mental Health Services</td>
<td>Center</td>
</tr>
<tr>
<td>1 Long Term Residential</td>
<td></td>
</tr>
</tbody>
</table>

**Usual care approaches:**
- 50% methadone, 50% clonidine
- 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)

<table>
<thead>
<tr>
<th></th>
<th>Bup/Nx</th>
<th>Clonidine</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Sex No. (%)</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>61</td>
<td>58</td>
<td>60</td>
</tr>
<tr>
<td>Female</td>
<td>39</td>
<td>42</td>
<td>40</td>
</tr>
<tr>
<td><strong>Race No. (%)</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>White</td>
<td>56</td>
<td>56</td>
<td>56</td>
</tr>
<tr>
<td>Black</td>
<td>19</td>
<td>19</td>
<td>19</td>
</tr>
<tr>
<td>Hispanic</td>
<td>12</td>
<td>17</td>
<td>16</td>
</tr>
<tr>
<td>Other</td>
<td>9</td>
<td>8</td>
<td>9</td>
</tr>
<tr>
<td><strong>Age in Years: Mean</strong></td>
<td>35.6</td>
<td>37.4</td>
<td>-</td>
</tr>
<tr>
<td>(Range 21-61)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Employed (%)</strong></td>
<td>-</td>
<td>-</td>
<td>66</td>
</tr>
<tr>
<td><strong>Mean Education in Years (SD)</strong></td>
<td>-</td>
<td>-</td>
<td>12.8 (1.7)</td>
</tr>
<tr>
<td><strong>Mean Years of Heroin Use (SD)</strong></td>
<td>-</td>
<td>-</td>
<td>6.6 (8.1)</td>
</tr>
<tr>
<td>Present and opioid neg</td>
<td>Bup/Nx (N)</td>
<td>%</td>
<td>Clonidine (N)</td>
</tr>
<tr>
<td>------------------------</td>
<td>------------</td>
<td>-------</td>
<td>---------------</td>
</tr>
<tr>
<td>N</td>
<td>77</td>
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<tr>
<td>Day 3 or 4</td>
<td>52</td>
<td>67.5</td>
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<tr>
<td>Day 7 or 8</td>
<td>63</td>
<td>81.8</td>
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<tr>
<td>Day 10 or 11</td>
<td>56</td>
<td>72.7</td>
<td>10</td>
</tr>
<tr>
<td>Day 13 or 14</td>
<td>59</td>
<td>76.6</td>
<td>8</td>
</tr>
</tbody>
</table>
Present and Opioid Negative 0001 (Inpatient)

Day 3-4 | Day 7-8 | Day 10-11 | Day 13-14
--- | --- | --- | ---
Clonidine | Bup/Nx

Day 3-4 | Day 7-8 | Day 10-11 | Day 13-14
--- | --- | --- | ---
Clonidine | Bup/Nx
## Demographics 0002 (Outpatient)

<table>
<thead>
<tr>
<th></th>
<th>Bup/Nx</th>
<th>Clonidine</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sex No. (%)</td>
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<td></td>
</tr>
<tr>
<td>Male</td>
<td>73</td>
<td>69</td>
<td>72</td>
</tr>
<tr>
<td>Female</td>
<td>27</td>
<td>31</td>
<td>28</td>
</tr>
<tr>
<td>Race No. (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>White</td>
<td>40</td>
<td>40</td>
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<tr>
<td>Black</td>
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<td>28</td>
<td>37</td>
</tr>
<tr>
<td>Hispanic</td>
<td>21</td>
<td>13</td>
<td>20</td>
</tr>
<tr>
<td>Other</td>
<td>3</td>
<td>3</td>
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</tr>
<tr>
<td>Age in Years: Mean</td>
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<td></td>
<td></td>
</tr>
<tr>
<td>(Range 21-61)</td>
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<td>40.0</td>
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<tr>
<td>Employed (%)</td>
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<td>56.8</td>
</tr>
<tr>
<td>Mean Education in Years (SD)</td>
<td>-</td>
<td>-</td>
<td>12.4 (2.1)</td>
</tr>
<tr>
<td>Mean Years of Heroin Use (SD)</td>
<td>-</td>
<td>-</td>
<td>9.4 (9.6)</td>
</tr>
<tr>
<td>Present and opioid neg</td>
<td>Bup/Nx (N)</td>
<td>%</td>
<td>Clonidine (N)</td>
</tr>
<tr>
<td>------------------------</td>
<td>------------</td>
<td>----</td>
<td>---------------</td>
</tr>
<tr>
<td>N</td>
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<td>Day 7 or 8</td>
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<td>Day 10 or 11</td>
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<tr>
<td>Day 13 or 14</td>
<td>46</td>
<td>29.3</td>
<td>4</td>
</tr>
</tbody>
</table>
Present and Opioid Negative
0002 (Outpatient)

Day 3-4  Day 7-8  Day 10-11  Day 13-14

Clonidine  Bup/Nx
NNT: Number Needed to Treat

CTN 0001 (Inpatient)

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

\[ \text{NNT Clonidine : BupNx} = 3.44 \]

CTN 0002 (Outpatient)

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

\[ \text{NNT Clonidine : Bup/Nx} = 5.44 \]

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