Short-Term Opioid Withdrawal Using Buprenorphine

Findings and strategies from a NIDA Clinical Trials Network Study
According to the Webster Dictionary definition

**To Blend** means:

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

http://www.merriam-webster.com/dictionary/blend
NIDA/SAMHSA Blending Initiative

- Developed in 2001 by NIDA and SAMHSA/CSAT, the initiative was designed to meld science and practice to improve 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.

- 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.
Blending Team Members

<table>
<thead>
<tr>
<th>Name</th>
<th>Position and Node</th>
</tr>
</thead>
<tbody>
<tr>
<td>Thomas Freese, Ph.D.</td>
<td>Chair – Pacific Southwest ATTC</td>
</tr>
<tr>
<td>Greg Brigham, Ph.D.</td>
<td>CTN Ohio Valley Node</td>
</tr>
<tr>
<td>Beth Finnerty, M.P.H.</td>
<td>Pacific Southwest ATTC</td>
</tr>
<tr>
<td>Kay Gresham-Morrison, LCSW, ACSW</td>
<td>Southeast ATTC</td>
</tr>
<tr>
<td>Judith Harrer, Ph.D.</td>
<td>CTN Ohio Valley Node</td>
</tr>
<tr>
<td>Dennis McCarty, Ph.D.</td>
<td>CTN Oregon Node</td>
</tr>
<tr>
<td>Susan Storti, Ph.D., R.N.</td>
<td>ATTC of New England</td>
</tr>
</tbody>
</table>

- ATTC representative
- NIDA researcher/Community treatment provider
Objectives for the Training

- Describe opioid withdrawal and the role of medical interventions during withdrawal
- Understand the results of new research on one strategy for helping patients withdraw from opioids using buprenorphine
- Define the procedures for using buprenorphine to conduct a 13-day opioid taper
So who are the participants in this endeavor?
An Introduction to SAMHSA/CSAT
CSAT’s Mission:

• To improve the lives of individuals and families affected by alcohol and drug abuse by ensuring access to clinically sound, cost-effective addiction treatment that reduces the health and social costs to our communities and the nation.

• CSAT's initiatives and programs are based on research findings and the general consensus of experts in the addiction field that, for most individuals, treatment and recovery work best in a community-based, coordinated system of comprehensive services.

• Because no single treatment approach is effective for all persons, CSAT supports the nation's effort to provide multiple treatment modalities, evaluate treatment effectiveness, and use evaluation results to enhance treatment and recovery approaches.
The ATTC Network
The ATTC Network
The Mission of the National Institute on Drug Abuse

• To lead the Nation in bringing the power of science to bear on drug abuse and addiction

• This charge has two critical components.
  - Strategic support and conduct of research across a broad range of disciplines
  - Ensuring the rapid and effective dissemination and use of the result of that research to significantly improve prevention, treatment and policy as it relates to drug use and addiction
So what is this thing called the CTN?
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 16 University-based Regional Research and Training Centers (RRTCs) involving 240 Community Treatment Programs (CTPs) in 23 states, Washington D.C., and Puerto Rico
CTN Node

Regional Research & Training Center

Community Treatment Program

Community Treatment Program

Community Treatment Program

Community Treatment Program

Community Treatment Program

Community Treatment Program
The Medications

Buprenorphine and Clonidine
Partial vs. Full Opioid Agonist and Antagonist

**Full Agonist**
(e.g., methadone)

**Partial Agonist**
(e.g. buprenorphine)

**Antagonist**
(e.g. naloxone)
Buprenorphine

• Partial Opioid Agonist
  - Has effects of typical opioid agonists at lower doses
  - Produces a ceiling effect at higher doses
  - Binds strongly to opioid receptor and is long-acting

• Safe and effective therapy for opioid maintenance and detoxification in adults

• Slow to dissociate from receptors so effects last even if one daily dose is missed (reduced effects may be felt few days after prolonged use).

• FDA approved for use with opioid dependent persons age 16 and older
Development of Tablet Formulations of Buprenorphine

- Buprenorphine is currently marketed for opioid treatment under the trade names:
  - Subutex® (buprenorphine)
  - 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
Clinical trials with opioid dependent adults have established the effectiveness of buprenorphine for the treatment of heroin addiction. Effectiveness of buprenorphine has been compared to:

- **Placebo** (Johnson et al., 1995; Kakko et al., 2003; Ling et al., 1998)
- **Methadone** (Fischer et al., 1999; Johnson, Jaffee, & Fudula, 1992; Schottenfield et al., 1997; Strain et al., 1994)
- **Methadone and LAAM** (levo-alpha-acetyl-methadol) (Johnson et al. 2000)
Buprenorphine Research Outcomes

• Buprenorphine is as effective as moderate doses of methadone (Fischer et al., 1999; Johnson, Jaffee, Fudula,. 1992; Ling et al., 1996; Schottenfield et al., 1997; Strain et al., 1994).

• Buprenorphine is as effective as moderate doses of LAAM (Johnson et al., 2000).

• Buprenorphine's partial agonist effects make it mildly reinforcing, encouraging medication compliance (Ling et al., 1998).

• After a year of buprenorphine plus counseling, 75% of patients retained in treatment compared to 0% in a placebo-plus-counseling condition (Kakko et al., 2003).
Why did they make two formulations?

Buprenorphine/Naloxone

Buprenorphine
Advantages of Buprenorphine/Naloxone

- Discourages IV use
- Diminishes diversion
Use of Buprenorphine: Studies on Cost-Effectiveness

- Medication costs are only one factor. Costs of providing treatment also include costs associated with clinic visits, staff time, etc. These costs are greater for methadone.

- While not yet studied in young adults, research on adult populations has demonstrated cost effectiveness of buprenorphine across several indicators.
Use of Buprenorphine: Studies on Cost-Effectiveness

- A cost effective comparison of buprenorphine versus methadone for opioid dependence both demonstrated increases in heroin-free days.

- There no statistical significance between the cost-effectiveness for buprenorphine and methadone.

(Doran et al., 2003)
Use of Buprenorphine: Studies on Cost-Effectiveness, cont’

- Treatment with buprenorphine-naloxone was associated with a reduction in opioid utilization and cost in the first year of follow-up (Kaur & McQueen, 2008).

- Systematic review found good studies supporting buprenorphine as a cost effective approach to opioid treatment (Doran, 2008).
Another study in Australia found buprenorphine demonstrated **lower crime costs and higher quality adjusted life years (QALY)**, concluding the likelihood of net benefits from substituting buprenorphine for methadone.

(Harris, Gospodarevshaya, & Ritter, 2005)
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>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>

(Chaing & Hawks, 2003)
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
Clonidine

- Clonidine - Catapress®
- Not a scheduled medication
- No special license required
- Standard clinical medication for opioid withdrawal
- Inpatient and outpatient settings
- Partially suppresses symptoms of opioid withdrawal (e.g., nausea, vomiting, sweating, diarrhea); however NOT effective in alleviating subjective effects of opioid withdrawal (e.g., body aches, abdominal cramps, cravings, etc.)
Contraindications for Use of Clonidine

- Pregnancy
- Liver damage
- History of auditory hallucinations of delirium
- Systolic blood pressure < 90 mm Hg
- Recent myocardial infarction
- Chronic renal failure
- History of hypertension, hypotension, fainting, or dizziness on rising
Medically – Assisted Withdrawal

(a.k.a. Dose Tapering; a.k.a. Detoxification)
Withdrawal

A period during which somebody addicted to a drug or other addictive substance stops taking it, causing the person to experience painful or uncomfortable symptoms

OR

A person takes a similar substance in order to avoid experiencing the effects described above
Withdrawal Syndrome

• Intensity varies with level & chronicity of use

• Cessation of opioids causes a rebound in function altered by chronic use

• Duration of withdrawal is dependent upon the half-life of the drug used:
  – Peak of withdrawal occurs 36 to 72 hours after last dose
  – Acute symptoms subside over 3 to 7 days
  – Protracted symptoms may linger for weeks or months
Medically-Assisted Withdrawal

- Relieves withdrawal symptoms while patients adjust to a drug-free state
- Can occur in an inpatient or outpatient setting
- Typically occurs under the care of a physician or medical provider
- Serves as a precursor to behavioral treatment, because it is designed to treat the acute physiological effects of stopping drug use
Principles of Medically-Assisted Withdrawal

- Complete an initial assessment
  - medical and psychiatric
  - alcohol and/or drug history
  - prior withdrawal experiences
- Pharmacologic management of withdrawal
- Utilization of ancillary medications
- Provision of psychological support
Why the Focus on Medically-Assisted Withdrawal (Detoxification)?

- Little data have been generated for the shorter-term use of BUP/NX for medically-assisted opioid withdrawal.
- However, studies are needed to determine strategies for assisting with withdrawal.
- The diversity of clinics in the CTN provides an unparalleled opportunity to conduct such a clinical endeavor.
The Research:
CTN Protocols 0001 and 0002
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
NIDA CTN 0001/0002 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

<table>
<thead>
<tr>
<th>6 Inpatient</th>
<th>6 Outpatient</th>
</tr>
</thead>
<tbody>
<tr>
<td>2 Therapeutic Communities</td>
<td>4 Opioid Treatment Programs</td>
</tr>
<tr>
<td>1 Free-standing, Chemical Dependency Hospital</td>
<td>1 HMO</td>
</tr>
<tr>
<td>2 Detox Units with Integrated Addiction and Mental Health Services</td>
<td>1 Community Mental Health Center</td>
</tr>
<tr>
<td>1 Long Term Residential</td>
<td></td>
</tr>
</tbody>
</table>

**Usual care approaches:**

- 50% methadone, 50% clonidine

**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?
<table>
<thead>
<tr>
<th>Demographics 0001 (Inpatient)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
</tr>
<tr>
<td>Sex No. (%)</td>
</tr>
<tr>
<td>Male</td>
</tr>
<tr>
<td>Bup/Nx</td>
</tr>
<tr>
<td>Clonidine</td>
</tr>
<tr>
<td>Total</td>
</tr>
<tr>
<td>Female</td>
</tr>
<tr>
<td>Bup/Nx</td>
</tr>
<tr>
<td>Clonidine</td>
</tr>
<tr>
<td>Total</td>
</tr>
<tr>
<td>Race No. (%)</td>
</tr>
<tr>
<td>White</td>
</tr>
<tr>
<td>Bup/Nx</td>
</tr>
<tr>
<td>Clonidine</td>
</tr>
<tr>
<td>Total</td>
</tr>
<tr>
<td>Black</td>
</tr>
<tr>
<td>Bup/Nx</td>
</tr>
<tr>
<td>Clonidine</td>
</tr>
<tr>
<td>Total</td>
</tr>
<tr>
<td>Hispanic</td>
</tr>
<tr>
<td>Bup/Nx</td>
</tr>
<tr>
<td>Clonidine</td>
</tr>
<tr>
<td>Total</td>
</tr>
<tr>
<td>Other</td>
</tr>
<tr>
<td>Bup/Nx</td>
</tr>
<tr>
<td>Clonidine</td>
</tr>
<tr>
<td>Total</td>
</tr>
<tr>
<td>Age in Years: Mean (Range 21-61)</td>
</tr>
<tr>
<td>Bup/Nx</td>
</tr>
<tr>
<td>Clonidine</td>
</tr>
<tr>
<td>Total</td>
</tr>
<tr>
<td>Employed (%)</td>
</tr>
<tr>
<td>Bup/Nx</td>
</tr>
<tr>
<td>Clonidine</td>
</tr>
<tr>
<td>Total</td>
</tr>
<tr>
<td>Mean Education in Years (SD)</td>
</tr>
<tr>
<td>Bup/Nx</td>
</tr>
<tr>
<td>Clonidine</td>
</tr>
<tr>
<td>Total</td>
</tr>
<tr>
<td>Mean Years of Heroin Use (SD)</td>
</tr>
<tr>
<td>Bup/Nx</td>
</tr>
<tr>
<td>Clonidine</td>
</tr>
<tr>
<td>Total</td>
</tr>
</tbody>
</table>
## Present and Opioid Negative 0001 (Inpatient)

<table>
<thead>
<tr>
<th>Present and opioid neg</th>
<th>Bup/Nx (N)</th>
<th>%</th>
<th>Clonidine (N)</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>N</td>
<td>77</td>
<td></td>
<td>36</td>
<td></td>
</tr>
<tr>
<td>Day 3 or 4</td>
<td>52</td>
<td>67.5</td>
<td>16</td>
<td>44.4</td>
</tr>
<tr>
<td>Day 7 or 8</td>
<td>63</td>
<td>81.8</td>
<td>13</td>
<td>36.1</td>
</tr>
<tr>
<td>Day 10 or 11</td>
<td>56</td>
<td>72.7</td>
<td>10</td>
<td>27.8</td>
</tr>
<tr>
<td>Day 13 or 14</td>
<td>59</td>
<td>76.6</td>
<td>8</td>
<td>22.2</td>
</tr>
</tbody>
</table>
Present and Opioid Negative 0001 (Inpatient)

% of Individuals present at end of taper

% of opioid free urines

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><strong>Sex No. (%)</strong></td>
<td></td>
<td></td>
<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><strong>Race No. (%)</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>White</td>
<td>40</td>
<td>40</td>
<td>40</td>
</tr>
<tr>
<td>Black</td>
<td>36</td>
<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>
<td>3</td>
</tr>
<tr>
<td><strong>Age in Years: Mean</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>(Range 21-61)</td>
<td>38.3</td>
<td>40.0</td>
<td></td>
</tr>
<tr>
<td><strong>Employed (%)</strong></td>
<td></td>
<td></td>
<td>56.8</td>
</tr>
<tr>
<td><strong>Mean Education in Years (SD)</strong></td>
<td>-</td>
<td>-</td>
<td>12.4 (2.1)</td>
</tr>
<tr>
<td><strong>Mean Years of Heroin Use (SD)</strong></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>
<td>157</td>
<td>74</td>
<td>5</td>
</tr>
<tr>
<td>Day 3 or 4</td>
<td>37</td>
<td>23.6</td>
<td>5</td>
</tr>
<tr>
<td>Day 7 or 8</td>
<td>56</td>
<td>35.7</td>
<td>6</td>
</tr>
<tr>
<td>Day 10 or 11</td>
<td>52</td>
<td>33.1</td>
<td>5</td>
</tr>
<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)

% of Individuals present at end of taper

% of opioid free urines

Day 3-4  |  Day 7-8  |  Day 10-11  |  Day 13-14
----------|-----------|-------------|-----------
Clonidine | Bup/Nx    |             |           
90  | 80  | 70  | 60  | 50  | 40  | 30  | 20  | 10  | 0  |

Day 3-4

Day 7-8

Day 10-11

Day 13-14
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
Protocol

Designed to examine the use of Suboxone® (buprenorphine/naloxone) versus the use of clonidine in a short-term opioid withdrawal, in inpatient and outpatient settings
The results of the protocols were pretty dramatic...
Outcomes

• The taper was successful in both outpatient and inpatient settings

• Buprenorphine/naloxone was superior to clonidine in both settings

• Inpatient setting: 76% of buprenorphine/naloxone patients vs. 22% of clonidine patients present and opioid clean at day 13

• Outpatient setting: 29% of buprenorphine/ naloxone patients vs. 5% of clonidine patients present and opioid clean at day 13
...so if I want to do this, what steps do I take?
First, the patient must be screened for appropriateness for buprenorphine treatment.
Screening Assessment Used in the CTN Protocols

- Medical history
- History of prior medication use
- Psychiatric evaluation
- DSM-IV checklist for substance dependence
- HIV risk assessment
- Hepatitis B and C Serology
Safety Assessment
Used in the CTN Protocols

- Physical examination
- Vital signs
- Blood chemistry
- Hematology
- Urinalysis
- 12 Lead electrocardiograph (ECG)
- Pregnancy test
Once you determine that buprenorphine is the best treatment...

... the next step is induction
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.

![Graph showing intrinsic activity vs. log dose of opioid, indicating maintenance level and dosage level.](image-url)
Transferring Patients Onto Buprenorphine: 3 Ways Significant Withdrawal Could Occur

Dose too low?

Insufficient agonist effects

Not full agonist

May not fully replace
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 replace

- **Precipitates Withdrawal**
  - Ceiling effect
Buprenorphine will replace other opioids at the receptor site; therefore, the patient experiences withdrawal.
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.
Five Steps to Starting Bup/Nx

1. Have patient **abstain** or impose ~ 8 hr. interval between prior agonist use and buprenorphine administration

2. **Mild withdrawal** symptoms optimal

3. Verify that the urine sample is **methadone-negative**

4. **Select** appropriate substitution dose

5. Start with **low dose** and **increase** over several days
The Dosing Schedule
Day 1 Dose Induction

- A split dose can be provided on day 1
- Tablets take 2-10 minutes to dissolve under the tongue.

<table>
<thead>
<tr>
<th>Bup-Nx DOSE</th>
<th>Day 1</th>
<th>Day 2</th>
<th>Day 3</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>4/1 + 4/1</td>
<td>8/2</td>
<td>16/4</td>
</tr>
</tbody>
</table>
# BUP-NX Taper Schedule

<table>
<thead>
<tr>
<th>Day</th>
<th>Bup/Nx Dose (mg of bup)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>4 (+ 4 if needed)</td>
</tr>
<tr>
<td>2</td>
<td>8</td>
</tr>
<tr>
<td>3</td>
<td>16</td>
</tr>
<tr>
<td>4</td>
<td>14</td>
</tr>
<tr>
<td>5</td>
<td>12</td>
</tr>
<tr>
<td>6</td>
<td>10</td>
</tr>
<tr>
<td>7</td>
<td>8</td>
</tr>
<tr>
<td>8-9</td>
<td>6</td>
</tr>
<tr>
<td>10-11</td>
<td>4</td>
</tr>
<tr>
<td>12-13</td>
<td>2</td>
</tr>
</tbody>
</table>
The study was successful, but will it work for everyone?
Inclusion Criteria for the CTN Protocols

• Treatment-seeking males and non-pregnant and non-lactating females 15 years and older

• Meet DSM-IV criteria for opioid dependence and in need of medical assistance for opioid withdrawal

• Systolic blood pressure ≥100mm Hg, and pulse ≤56 bpm.

• Good general health or, in case of a medical/psychiatric condition needing ongoing treatment, under the care of a physician willing to continue patient’s medical management and cooperate with the study physicians
Inclusion Criteria for the CTN Protocols, cont’

• Agreeable to and capable of signing the informed consent approved by an institutional review board and, if under the age of 18 (excluding emancipated minors), assent and concurrent consent from a parent or legal guardian

• Use of one of the following acceptable methods of birth control by female patients of childbearing potential:
  - oral contraceptives
  - barrier (diaphragm/cervical cap) with spermicide or condom
  - intrauterine progesterone contraceptive system
  - levonorgestrel implant
  - medroxyprogesterone acetate contraceptive injection
  - complete abstinence from sexual intercourse
Exclusion Criteria for the CTN Protocols

- Medical conditions (i.e., active hepatitis, unstable cardiovascular disease, liver or kidney disease)
- Clinical significant abnormalities in ECG
- Allergy or sensitivity to buprenorphine, naloxone, or clonidine
- Receiving medications which may interact adversely with clonidine (e.g., calcium channel blockers, digitalis, beta-blockers)
- Acute severe psychiatric condition or imminent suicide risk
Exclusion Criteria for the CTN Protocols, cont’

- Dependence on alcohol, benzodiazepines, or other depressants or stimulants, requiring immediate medical attention
- Participation in another investigational study within the last 30 days
- Methadone or LAAM maintenance or detoxification within the 30 days of induction
- Pregnant, lactating, or planning to become pregnant
Ancillary Medications for Treatment of Withdrawal Symptoms
Ancillary Medications

- Use of ancillary medications fairly common during medically-assisted withdrawal
- Dispensing of medication at the physician’s discretion in accordance with clinical need
- Choice of medications limited
- Most patients received at least one ancillary medication during the study
Following is a list of the ancillary medications that were used for this protocol...

It is not clear what effect it will have if different medications are used.
Bone Pain and Arthralgias

- Acetaminophen 650 mg q 4-6 NTE 3900 in 24 hrs.
- Ibuprofen 800 mg q 8 w/food
- Methocarbamol (Robaxin) 500-1000 mg q6 hrs prn; NTE 2000 mg per 24 hrs.

Diarrhea

- Loperamide (Immodium) 2mg; NTE 8mg per 24 hrs.
- Donnatal 1-2 tablets q 6-8 hrs prn; NTE 8 tablets per 24 hrs.
Anxiety and Restlessness (use one of the following)

- Lorazepam (Ativan) 1-2 mg q 6 hrs. prn; NTE 8 mg per 24 hrs.
- Oxazepam (Serax) 15 - 30 mg po q 6 hrs. prn; NTE 120 mg per 24 hrs.
- Phenobarbital 15 - 30 mg po q 6 hrs. prn; NTE 120 mg per 24 hrs.
- Hydroxyzine hydrochloride (Atarax/Vistaril) 50 mg, po q 6 hrs. prn; NTE 200 mg per 24 hrs.
Ancillary Medications
Used in the CTN Protocols

**Nausea**
- Trimethobenzamide (Tigan) 250 mg q 8 hrs prn; NTE 750 mg per 24 hrs.

**Insomnia**
- Diphenhydramine (Benadryl) 25-50mg; NTE 300mg per 24 hrs.
- Zolpidem Tartrate (Ambien) 10mg, 1-3 tabs, po q hs prn
- Trazadone Hydrochloride (Desyrel) 50mg, 1 to 3 tabs, po q hs prn
- Doxepin Hydrochloride (Sinequan) 50mg, 1 to 3 tabs, po q hs prn
Ancillary Medication Use Among Patients Receiving Buprenorphine

- 19.7% of patients received no ancillary meds
- 80.3% received at least one ancillary med

<table>
<thead>
<tr>
<th>Insomnia</th>
<th>Bone Pain &amp; Arthralgias</th>
<th>Anxiety &amp; Restlessness</th>
<th>Nausea</th>
<th>Diarrhea</th>
</tr>
</thead>
<tbody>
<tr>
<td>62%</td>
<td>54%</td>
<td>52%</td>
<td>35%</td>
<td>25%</td>
</tr>
</tbody>
</table>

- Average of 2.3 withdrawal symptoms were treated

(Amass et al., 2004)
Ancillary Medication Use

Patients (%) Receiving Any Ancillary Med

Study Day

(Amass et al., 2004)
Adverse Events

That is, what additional symptoms did patients report?
Adverse Events

• Information about adverse events is collected in all medically-related research studies.

• Adverse events are defined as any untoward medical or psychiatric occurrence during the patient’s participation in the trial.

• Adverse events may or may not be related to the treatment being provided.

• By collecting adverse event information, data concerning side effects of the treatment is obtained.
Adverse Events

- Assessed daily during detoxification and at 1 month follow-up visit
- “How have you been feeling since I saw you last?”
- Instruments
  - Clinical Opiate Withdrawal Scale (COWS)
  - Adjective Rating Scale for Withdrawal (ARSW)
  - Visual Analog Report (VAS)
Number of Adverse Events for Total Sample and Completers

|                  | Total* | Completer | Total* | Completer*
<table>
<thead>
<tr>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Inpatient</td>
<td>2.4</td>
<td>1.6</td>
<td>1.2</td>
<td>0.6</td>
</tr>
<tr>
<td>Outpatient</td>
<td>1.5</td>
<td>1.1</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Bup Clonidine

p < 0.001
Eighteen individuals experienced serious side effects over the course of the clinical trial:

- 61% were associated with hospitalization for drug relapse or similarly related treatment

- 83% transpired during the follow-up period

- One death in the buprenorphine condition was secondary to respiratory failure resulting from a myocardial infarction

- One death in clonidine resulting from bacterial endocarditis

- One event – hematemesis, presumably due to bleeding of esophageal tear - possibly related to excessive hiccupping precipitated by the Suboxone®
The Role of Psychosocial Treatment During Medically-Assisted Opioid Withdrawal
The Role of Psychosocial Treatment

- Counseling is essential
- Medication + Therapy is needed to maximize therapeutic effects
- Use the patient handbook in addition to your site’s regular curriculum
Key Lessons Learned from the CTN Experience
Lessons Learned

1. Direct induction with BUP/NX is acceptable to a majority of opioid users. Ninety percent of patients completed induction, reaching a target dose of 16 mg within 3 days.

2. A substantial number of patients completed the short-term detox, regardless of setting or program philosophy. This program thus met a major goal of many programs to improve early treatment engagement. Short-term treatment can also help to establish an effective therapeutic alliance with local care providers.
3. Ancillary medications were provided to a majority of patients taking BUP/NX but mostly for protracted withdrawal symptoms common among patients withdrawing from opioids.

4. BUP/NX is safe for use in a wide range of community treatment settings. There were few serious adverse events and most were not related to BUP/NX.
5. **Patient interest** in the BUP/NX detox was high and some programs developed wait lists, suggesting that the **combination mixture will not deter patients** from seeking buprenorphine treatment.

6. **All sites expected patients to attend counseling** regularly. Whether short-term BUP/NX detox would fare as well in primary care or office based settings where such services are not on site is not known.
Lessons from Additional Analyses: Predictors of Treatment Success

- Medication was the best predictor of treatment outcome for opioid medically-assisted withdrawal regardless of treatment setting.
- Inpatient treatment was a strong predictor of treatment success.
- Those with greater reduction in opioid withdrawal severity from baseline to day 3 were more likely to have a positive treatment outcome.
- Those who did the best with clonidine had low severity withdrawal symptoms at baseline.

(Ziedonis et al., 2009)
Lessons from a Study of Longer and Shorter Taper Schedules

- Differences in being drug free at end taper did not differ for 7 or 28 day groups (after 4 week stabilization)

- A relatively quick taper may be advantageous and did not result in relapse to drug use at greater rates than longer tapers

- Patients stabilized physiologically on a range of buprenorphine doses can be tapered successfully over 7 days

- There was no advantage to prolonging the tapering schedule for weeks

(Ling et al., 2009)
More research is needed to answer questions such as:

- To what degree do these patients return to opioid use following taper?

- What counseling is best coupled with this taper?

- What difference would it make if the treatment were provided in a physician’s office rather than in a substance abuse treatment program or clinic where other ancillary services are available?
QUESTIONS?