Short-Term Opioid Withdrawal Using Buprenorphine

Findings and strategies from a NIDA Clinical Trials Network Study
NIDA/SAMHSA Blending Initiative

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.
NIDA/SAMHSA Blending Initiative:
Blending Team Members

- Thomas Freese, PhD – Chair – Pacific Southwest ATTC
- Greg Brigham, PhD – CTN Ohio Valley Node
- Beth Finnerty, MPH – Pacific Southwest ATTC
- Kay Gresham-Morrison, LCSW, ACSW – Southeast ATTC
- Judith Harrer, PhD – CTN Ohio Valley Node
- Dennis McCarty, PhD – CTN Oregon Node
- Susan Storti, PhD, RN – ATTC of New England

ATTC representative  |  NIDA researcher
Objectives for the Training

By participating in this training you will be able to do the following:

- Describe **opioid withdrawal** and the role of medical interventions in it
- 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**
Introductions

Introduce yourself by briefly providing the following information:

- Your name and the agency in which you work
- Experience with opioid treatment
- What you expect from the training
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
An Introduction to NIDA
NIDA's mission is to lead the Nation in bringing the power of science to bear on drug abuse 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 17 University-based Regional Research and Training Centers (RRTCs) involving 116 Community Treatment Programs (CTPs) in 24 states, Washington D.C., and Puerto Rico
The Medications

**Buprenorphine** and **Clonidine**
Buprenorphine

- 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 opioid receptor and is long-acting

- Safe and effective therapy for opioid maintenance and detoxification
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 levo-alpha-acetyl-methadol (LAAM) (Johnson et al. 2000)
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 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.
Opioid Partial Agonists

- Buprenorphine – Buprenex®, Suboxone®, Subutex®
- Pentazocine - Talwin®
Buprenorphine/Naloxone Combination and Buprenorphine Alone
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
Advantages of Buprenorphine/Naloxone

- Discourages IV use
- Diminishes diversion
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

- 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®
- Inpatient and outpatient settings
- A centrally acting alpha 2-adrenergic agonist
- Partially suppresses peripheral symptoms of opioid withdrawal (e.g., nausea, vomiting, sweating, diarrhea) by decreasing autonomic nervous system activity
Why Use Clonidine?

- Not a scheduled medication
- No special license required
- Alleviates autonomic mediated signs and symptoms
- Standard clinical medication for opioid withdrawal
- Not effective in alleviating subjective effects of opioid withdrawal (e.g., body aches, abdominal cramps, cravings, etc.)
Contraindication 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

Goals of Medically-Assisted Withdrawal

- Provide a smooth transition from a physically dependent state to non-dependent state with medical supervision
- Provide withdrawal that is humane and thus protects the patient’s dignity
- Medically supervised withdrawal is accompanied with and followed by psychosocial treatment, and sometimes medication treatment (i.e., naltrexone) to minimize risk of relapse
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
Medically-Assisted Withdrawal

- 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
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
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

Oregon
Kaiser Permanente

Pacific
Aegis

Ohio Valley
Midtown

New York
ARTC
Bellevue

Delaware Valley
Mercer
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>Community Treatment Programs</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>6 Inpatient</strong></td>
</tr>
<tr>
<td>2 Therapeutic Communities</td>
</tr>
<tr>
<td>1 Free-standing, Chemical Dependency Hospital</td>
</tr>
<tr>
<td>2 Detox Units with Integrated Addiction and Mental Health Services</td>
</tr>
<tr>
<td>1 Long Term Residential</td>
</tr>
<tr>
<td><strong>Usual care approaches:</strong></td>
</tr>
<tr>
<td>50% methadone, 50% clonidine</td>
</tr>
<tr>
<td><strong>6 Outpatient</strong></td>
</tr>
<tr>
<td>4 Opioid Treatment Programs</td>
</tr>
<tr>
<td>1 HMO</td>
</tr>
<tr>
<td>1 Community Mental Health Center</td>
</tr>
<tr>
<td><strong>Usual care approaches:</strong></td>
</tr>
<tr>
<td>methadone in OTPs and clonidine in HMO</td>
</tr>
</tbody>
</table>
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>
</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)

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

Clonidine
Bup/Nx
<table>
<thead>
<tr>
<th>demographic</th>
<th>Bup/Nx</th>
<th>Clonidine</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sex No. (%)</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>Race No. (%)</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>Age in Years: Mean</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>Employed (%)</td>
<td></td>
<td></td>
<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>
</tbody>
</table>
## Present and Opioid Negative 0002 (Outpatient)

<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>157</td>
<td></td>
<td>74</td>
<td></td>
</tr>
<tr>
<td>Day 3 or 4</td>
<td>37</td>
<td>23.6</td>
<td>5</td>
<td>6.8</td>
</tr>
<tr>
<td>Day 7 or 8</td>
<td>56</td>
<td>35.7</td>
<td>6</td>
<td>8.1</td>
</tr>
<tr>
<td>Day 10 or 11</td>
<td>52</td>
<td>33.1</td>
<td>5</td>
<td>6.8</td>
</tr>
<tr>
<td>Day 13 or 14</td>
<td>46</td>
<td>29.3</td>
<td>4</td>
<td>5.4</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

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
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

- Insufficient agonist effects
- Dose too low?
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.
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**

<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>

- A split dose can be provided on day 1
- Tablets take 2-10 minutes to dissolve under the tongue.
# 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 $\geq 100$ mm Hg, and pulse $\geq 56$ 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
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 (continued)

- 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 q4-6 NTE 3900 in 24 hrs.
- **Ibuprofen** 800 mg q8 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.
- **Donnataal** 1-2 tablets q 6-8 hrs prn; NTE 8 tablets per 24 hrs.
Ancillary Medications Used in the CTN Protocols

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 q6 hrs. prn; NTE 120 mg per 24 hrs.
- **Phenobarbital** 15 - 30 mg po q6 hrs. prn; NTE 120 mg per 24 hrs.
- **Hydroxyzine hydrochloride (Atarax/Vistaril)** 50 mg, po q6 hrs. prn; NTE 200 mg per 24 hrs.
Ancillary Medications Used in the CTN Protocols

Nausea

- **Trimethobenzamide (Tigan)** 250 mg q8 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 qhs prn
- **Trazadone Hydrochloride (Desyrel)** 50mg, 1 to 3 tabs, po qhs prn
- **Doxepin Hydrochloride (Sinequan)** 50mg, 1 to 3 tabs, po qhs 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>Condition</th>
<th>Percentage</th>
</tr>
</thead>
<tbody>
<tr>
<td>Insomnia</td>
<td>62%</td>
</tr>
<tr>
<td>Bone Pain &amp; Arthralgias</td>
<td>54%</td>
</tr>
<tr>
<td>Anxiety &amp; Restlessness</td>
<td>52%</td>
</tr>
<tr>
<td>Nausea</td>
<td>35%</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>25%</td>
</tr>
</tbody>
</table>

Average of 2.3 withdrawal symptoms were treated.

Source: Amass et al. (2004) The American Journal on Addictions
Ancillary Medication Use

Patients (%) Receiving Any Ancillary Med.

Study Day

- Insomnia
- Anxiety and Restlessness
- Bone Pain and Arthralgias
- Nausea
- Diarrhea

Source: Amass et al. (2004) The American Journal on Addictions
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

- Inpatient
  - Total*: 1.5
  - Completer: 1.6
- Outpatient
  - Total*: 0.7
  - Completer: 0.6
  - p < 0.001

Bup

Clonidine
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.