

# ***Short Term Opioid Withdrawal Using Buprenorphine***





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# ***Short Term Opioid Withdrawal Using Buprenorphine***

## **Introduction to the Training**

### **Background Information: NIDA-SAMHSA Blending Initiative**

In order to disseminate information to the addiction treatment field, the National Institute on Drug Abuse (NIDA) has created a partnership with the Addiction Technology Transfer Center (ATTC) Network. The ATTCs are funded by the Substance Abuse and Mental Health Services Administration (SAMHSA). The fourteen regional ATTCs throughout the country and the ATTC National Office provide specialized training and technical assistance to substance abuse treatment professionals in order to create a more effective treatment workforce. NIDA provided additional support to the ATTC Network and thereby established the NIDA-SAMHSA Blending Initiative. Through this initiative, special groups called Blending Teams composed of NIDA researchers and ATTC representatives meet to design dissemination strategies.

### **Focus on Buprenorphine**

In the year 1999, NIDA created the Clinical Trials Network (CTN). The CTN conducts studies of behavioral, pharmacological, and integrated behavioral and pharmacological treatment interventions in rigorous, multi-site clinical trials to determine effectiveness across a broad range of community-based treatment settings and diverse patient populations. Once research is completed, the CTN will work to transfer the research results to physicians, providers, and their patients to improve the quality of drug abuse treatment throughout the country.

In 2002 tablet formulations of buprenorphine were approved by the FDA for the treatment of opiate addiction. Additionally, the CTN has implemented and completed two clinical trials comparing a short-term opioid withdrawal using buprenorphine versus clonidine in both inpatient and outpatient settings. The results of these trials suggest that buprenorphine is substantially better than clonidine for opioid detoxification.

The results of these trials strongly supported this method of using buprenorphine.

In order to prepare the field to effectively integrate this treatment method into their current practice, NIDA formed a Blending Team to develop a package of training materials to instruct providers to implement the procedures evaluated through these research protocols.

This training assumes some basic information about what buprenorphine is and how it is used. One way that this information can be attained is by participating in another training developed through the NIDA/SAMHSA Blending Initiative-- ***Buprenorphine Treatment: A Training for Multidisciplinary Addiction Professionals (Buprenorphine Awareness)***. This awareness training is designed for multidisciplinary (non-physician) addiction professionals to educate them about buprenorphine and its use in the treatment of opioid addiction. This training was designed to provide a broad overview of the medication, its effects, and the role of non-physician practitioners in providing and supporting the treatment of individuals receiving this medication.

## Blending Team Members

Thomas Freese, Ph.D. – Pacific Southwest ATTC – Blending Team Chair

Greg Brigham, Ph.D. – CTN Ohio Valley Node

Beth Finnerty, M.P.H. – Pacific Southwest ATTC

Kay Gresham-Morrison, LCSW, ACSW – Southeast ATTC

Judith Harrer, Ph.D. – CTN Ohio Valley Node

Dennis McCarty, Ph.D. – CTN Oregon Node

Susan Storti, Ph.D., R.N. – ATTC of New England

## What Does the Training Package Contain?

- PowerPoint Training Slides
- Trainer's Manual
- Marketing Brochure

## What Does This Trainer's Manual Contain?

This training manual, ***Short Term Opioid Withdrawal Using Buprenorphine***, is the product of the NIDA/SAMHSA Blending Team. The manual is designed to support a half-day face-to-face training to review the results from research conducted by the NIDA Clinical Trials Network examining a 13-day buprenorphine versus clonidine in both inpatient and outpatient settings. The training will then provide instruction for implanting this protocol into treatment settings including methods of evaluation and induction, the taper schedule and use of ancillary medications during treatment. The training may be incorporated into the Buprenorphine Awareness training or adapted in other ways by ATTC and other trainers across the country to meet the needs of their local region. Therefore, detailed speaker notes, not a word-for-word script, are provided to allow for maximum flexibility. Comments in italics are for the trainer only, and are not meant to be read aloud.

## How Are the PowerPoint Training Slides Organized?

The training package is designed to provide information and content for a four-hour training. The training should be adapted by adding additional information to meet the needs of the audience.

This course, ***Short Term Opioid Withdrawal Using Buprenorphine***, begins by providing the results of the research on which the training is based. This sets the stage for the information that is presented later in the course by providing information about why buprenorphine is being used and the outcomes of this methods for tapering people off of opioids. The course will then provide an overview of opioid withdrawal and symptoms that patients experience during withdrawal. The role of buprenorphine in managing withdrawal will then be discussed. Finally, the training will provide a step-by-step guide for delivering this 13-day taper as it was implemented and evaluated in two CTN protocols.

Adaptation of these materials to meet the needs of the specific target audience is expected. It is essential that the trainers identify the extent of the attendees' background and experience with opioid treatment, generally and with using buprenorphine in treatment. For instance, if the training audience is a group of physicians who are already prescribing buprenorphine, extensive discussion about opioid withdrawal may not be warranted. Instead, this section

could be replaced with a discussion of the experience of inducting the patients onto the medication.

The training is designed to be delivered in about four hours. As a rule of thumb, the training should be paced to allow approximately two minutes for each slide.

### **General Information about Conducting the Training**

The training can be conducted in any sized group, but small- to medium-sized groups (10-25 people) are recommended. Smaller sized groups will ensure adequate time for discussion and exploration of questions and concerns with the participants.

### **Materials Needed to Conduct the Training**

- LCD projector to project the PowerPoint training slides OR printed overheads and overhead projector
- Computer, laptop or similar device to run the PowerPoint slideshow
- Flip chart paper and easel/white board, and pens to write down relevant information.

### **Overall Training Notes**


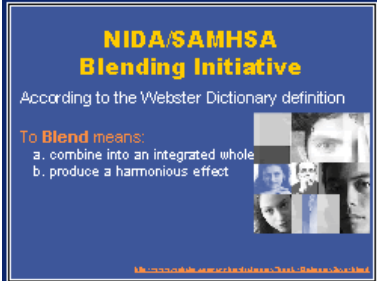

Attempt to find as much out about the trainees as possible prior to the training. This will help the trainer(s) to customize the presentation and avoid reviewing information that will seem elementary or redundant to the participants.


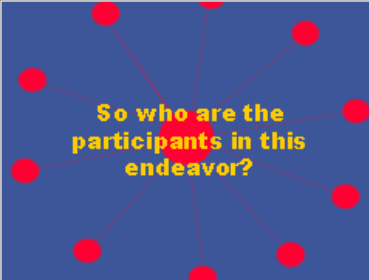
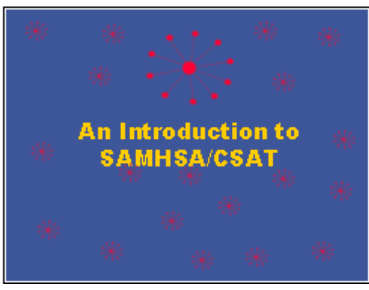
It is highly recommended that training be conducted or co-trained with a physician or other medical personnel who have experience with buprenorphine treatment. If the trainer can pair with one of the physicians who were part of the original CTN studies this would be even better as they would be able to speak directly about their experience with the implementation of the protocol described in this training package. At minimum, the trainer must have adequate knowledge and experience to discuss some of the basic physical symptoms associated with medically assisted withdrawal from opioids and have a relationship with a physician with whom they can consult if more detailed medical questions arise during the training.



## Short Term Opioid Withdrawal Using Buprenorphine Slide-By-Slide Trainer Notes

The notes below contain information that can be presented with each slide. This information is designed as a guidepost and can be adapted to meet the needs of the local training situation. Information can be added or deleted at the discretion of the trainer(s).

 <p><b>Short-Term Opioid Withdrawal Using Buprenorphine</b> Findings and strategies from a NIDA Clinical Trials Network Study</p>	<p><b>Slide 1: Short Term Opioid Withdrawal Using Buprenorphine</b></p> <p>Welcome participants and take care of housekeeping details such as location of restrooms, turning off cell phones, participate actively, etc.</p> <p><i>Briefly describe the development of the Blending Team product, as well as the purpose of the training as described above in the introduction to this manual.</i></p> <p><i>It is important to note that this training is focused on educating people about one way of conducting opioid detoxification. The training will review some basic information about buprenorphine, but participants will gain a better understanding of these methods if they already have a basic understanding of the medication and its mechanism of action.</i></p>
 <p><b>NIDA/SAMHSA Blending Initiative</b> According to the Webster Dictionary definition</p> <p>To <b>Blend</b> means: a. combine into an integrated whole b. produce a harmonious effect</p>	<p><b>Slide 2: NIDA/SAMHSA Blending Initiative</b></p> <p>Read the definition of “Blend.”</p> <p>Indicate that what NIDA wanted to do with the creation of the Blending Teams was to accomplish these two things. To combine the strengths of NIDA’s research experience with SAMHSA’s expertise in information dissemination to produce a harmonious effect in the field of substance abuse treatment.</p>
 <p><b>NIDA/SAMHSA Blending Initiative</b></p> <ul style="list-style-type: none"> <li>Developed in 2001 by NIDA and SAMHSA/CSAT, the initiative was designed to <b>meld science and practice</b> together to improve drug abuse and addiction treatment.</li> <li>“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.</li> <li>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.</li> </ul>	<p><b>Slide 3: NIDA/SAMHSA Blending Initiative</b></p> <p><b>Introduce the concept of the NIDA/SAMHSA Blending Teams – mostly based on research coming out of CTN</b></p> <p>Other examples of NIDA Blending Team Products currently available include a buprenorphine awareness training targeting non-physician practitioners (Buprenorphine Treatment: A Training for Multidisciplinary Addiction Professionals)</p>

<p><b>NIDA/SAMHSA Blending Initiative: Blending Team Members</b></p> <ul style="list-style-type: none"> <li>• Thomas Freese, Ph.D. – Chair – PacificSouthwest IATTC</li> <li>• Greg Brigham, Ph.D. – CTM Ohio Valley Node</li> <li>• Beth Finnerty, M.P.H. – PacificSouthwest IATTC</li> <li>• Kay Gresham-Morrison, LCSW, ACSW – Southeast IATTC</li> <li>• Judith Hamer, Ph.D. – CTM Ohio Valley Node</li> <li>• Dennis McCarty, Ph.D. – CTM Oregon Node</li> <li>• Susan Storti, Ph.D., R.N. – ATTC of New England</li> </ul> <p>ATTC representatives      NIDA researcher</p>	<p><b>Slide 4: NIDA-SAMHSA Blending Initiative: Blending Team Members</b></p> <p>Acknowledge the members of the Blending Team who created these materials.</p> <p>Note that the membership consisted of a chair from the ATTC network plus three ATTC representatives and three NIDA researchers.</p>
<p><b>Objectives for the Training</b></p> <ul style="list-style-type: none"> <li>• By participating in this training you will be able to do the following:</li> <li>• Describe <i>opioid withdrawal</i> and the role of medical interventions in it</li> <li>• Understand the <i>results of new research</i> on one strategy for helping patients withdraw from opioids using buprenorphine</li> <li>• Define the <i>procedures</i> for using buprenorphine to conduct a 13-day opioid taper</li> </ul>	<p><b>Slide 5: Objectives for the Training</b></p>
<p><b>Introductions</b></p> <ul style="list-style-type: none"> <li>• Introduce yourself by briefly providing the following information: <ul style="list-style-type: none"> <li>• Your name and the agency in which you work</li> <li>• Experience with opioid treatment</li> <li>• What you expect from the training</li> </ul> </li> </ul> 	<p><b>Slide 6: Introductions</b></p> <p><i>Begin the training by asking participants to briefly introduce themselves by providing their name and the agency for which they work, their experience with opioid treatment, and what they expect to gain from the training.</i></p> <p>Example Ice Breaker – Raise your hand if you:</p> <ul style="list-style-type: none"> <li>• Work primarily or exclusively with opioid addicted individuals</li> <li>• Work as a substance abuse counselor</li> <li>• Work as medical personnel</li> </ul>
<p><b>So who are the participants in this endeavor?</b></p> 	<p><b>Slide 7: So who are the participants in this endeavor?</b></p> <p>So now we will introduce the key participants who helped put these materials together.</p>
<p><b>An Introduction to SAMHSA/CSAT</b></p> 	<p><b>Slide 8: An Introduction to SAMHSA/CSAT</b></p> <p>The Center for Substance Abuse Treatment (CSAT) of the Substance Abuse and Mental Health Services Administration (SAMHSA), U.S. Department of Health and Human Services (DHHS), was created in October 1992 with a congressional mandate to expand the availability of effective treatment and recovery services for alcohol and drug problems.</p>

**SAMHSA/CSAT**

CSAT's Mission:

- To improve the lives of individuals and families affected by alcohol and drug abuse by ensuring access to timely, sound, cost-effective addiction treatment; reducing 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, focus on more individuals, treatment, and recovery work, and in a community-based, coordinated system of comprehensive services.
- Because no single treatment approach is effective for all persons, CSAT supports the nation's efforts to provide multiple preventive, rehabilitative, and aftercare treatment effectiveness, and use evaluation results to enhance treatment and recovery approaches.

**Slide 9: SAMHSA/CSAT**  
Read CSAT mission.

Highlight the importance of the research base in all of CSAT's programming and educating the field about the advances of science to continually improve the quality of services provided.

**The ATTC Network**

**Slide 10: The ATTC Network**

One of the major vehicles that SAMHSA has for ensuring that the workforce is adequately trained is the Addiction Technology Transfer Center Network.

**The ATTC Network**

**Slide 11: The ATTC Network**

Comprised of 14 regional centers and a national office, the ATTC Network is dedicated to identifying and advancing opportunities for improving addiction treatment.

Our vision is to unify science, education and services to transform the lives of individuals and families affected by alcohol and other drug addiction.

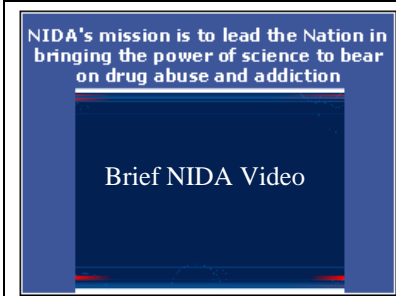
Serving the 50 U.S. states, the District of Columbia, Puerto Rico, the U.S. Virgin Islands and the Pacific Islands, the ATTC Network delivers cutting-edge knowledge and skills that develop a powerful workforce.

**An Introduction to NIDA**

**Slide 12: An Introduction to NIDA**

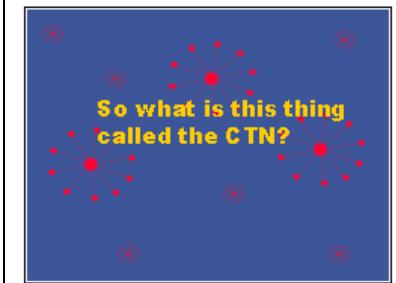
The National Institute on Drug Abuse (NIDA) was established in 1974, and in October 1992 it became part of the National Institutes of Health, Department of Health and Human Services.

Recent scientific advances have revolutionized our understanding of drug abuse and addiction. The majority of these advances, which have dramatic implications for how to best prevent and treat addiction, have been supported by the National Institute on Drug Abuse (NIDA).

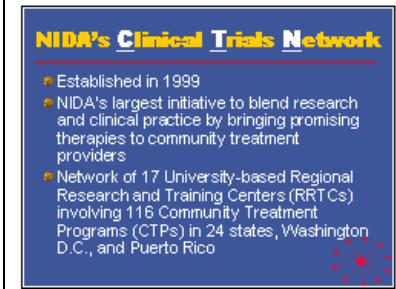


**Slide 13: The NIDA Mission**  
 NIDA is not only seizing upon unprecedented opportunities and technologies to further the understanding of how drugs of abuse affect the brain and behavior, but also *working to ensure the rapid and effective transfer of scientific data to policy makers, drug abuse practitioners, other health care practitioners, and the general public.* The scientific knowledge that is generated through NIDA research is a critical element to improving the overall health of the Nation. Our goal is to ensure that science, not ideology or anecdote, forms the foundation for all of our Nation's drug abuse reduction efforts.

*(After describing NIDA's mission, right click over the image on the slide and select "rewind" from the menu. Right click over the image again and select "play" from the menu)*



**Slide 14: So what is this thing called the CTN?**  
 To date, the efficacy of new treatments for drug addiction has been demonstrated primarily in specialized research settings, with somewhat restricted patient populations. To address this problem, the National Institute on Drug Abuse (NIDA) has established the National Drug Abuse Treatment Clinical Trials Network (CTN).

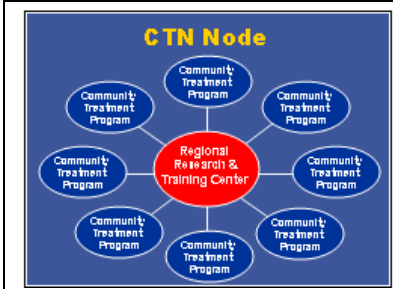


**Slide 15: NIDA's Clinical Trials Network**  
 The mission of the CTN is twofold:

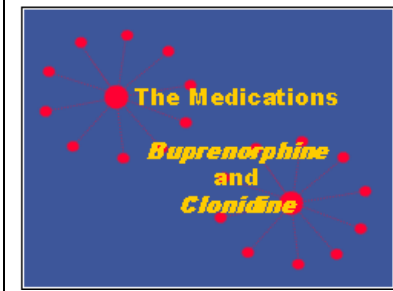
- Conduct studies of behavioral, pharmacological, and integrated behavioral and pharmacological treatment interventions of therapeutic effect in rigorous, multisite clinical trials to determine effectiveness across a broad range of community-based treatment settings and diversified patient populations; and
- Transfer the research results to physicians, providers, and their patients to improve the quality of drug abuse treatment throughout the country using science as the vehicle.



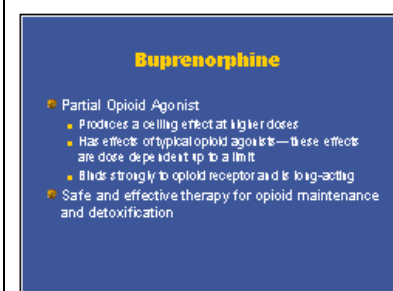
**Slide 16: CTN Nodes**  
 This map shows the current locations of the CTN RRTCs. The Dots indicate the locations of the Regional Research and Training Centers—these are the funded universities that oversee the research activities and provide training,  
 States with the orange borders are states where community treatment programs are located.



**Slide 17: CTN Node**  
 Each Node has one RRTC and 5 – 10 affiliated community treatment programs (CTP). CTN research is conducted in the CTPs. CTPs are chosen to participate in a given research protocol based on match between the study questions and requirements and the populations served by the CTP. For instance, in the buprenorphine studies, a CTP could be chosen if they served an opioid dependent population from whom they could recruit study participants.



**Slide 18: The Medications: Buprenorphine and Clonidine**  
 Before we discuss the specifics of the research conducted, we will spend a few minutes talking about the medications being investigated and why they were chosen.



**Slide 19: Buprenorphine**


The partial agonist properties of the medication are important to understand.

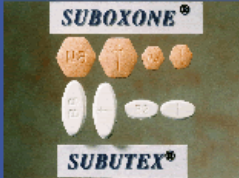
The effects of the medication at lower doses are virtually the same as that of full agonists. However, as the dose is increased, the effects level out for buprenorphine (especially respiratory suppression), where they continue to increase with full agonist medications. This is called a “ceiling effect.” This ceiling effect greatly decreases the risk of overdose when compared to full agonists.

Buprenorphine has a very HIGH affinity for opioid receptors. It displaces morphine, methadone, and other full agonist opioids from the receptor. Additionally buprenorphine dissociates slowly from the receptor.

This high affinity for and slow dissociation from the receptor result in buprenorphine blocking the effects of other opioids, such as heroin. Additionally, the high affinity and slow dissociation give rise to buprenorphine’s prolonged therapeutic effects and may also reduce the magnitude of withdrawal symptoms associated with buprenorphine dose reduction.

Clinical trials have demonstrated that buprenorphine is a safe and effective medication for both opioid maintenance and medically-assisted withdrawal (detoxification).

<p style="text-align: center;"><b>Buprenorphine: A Science-Based Treatment</b></p> <p>Clinical trials have established the effectiveness of buprenorphine for the treatment of heroin addiction. Effectiveness of buprenorphine has been compared to:</p> <ul style="list-style-type: none"> <li>• Placebo (Johnson et al. 1996; Ling et al. 1998; Kakko et al. 2003)</li> <li>• Methadone (Johnson et al. 1992; Strain et al. 1994a, 1994b; Ling et al. 1996; Schottenfield et al. 1997; Fischer et al. 1999)</li> <li>• Methadone and levo-alpha-acetyl-methadol (LAAM) (Johnson et al. 2000)</li> </ul>	<p><b>Slide 20: Buprenorphine: A Science-Based Treatment</b></p> <p>In the development of the medication, the effectiveness of buprenorphine has been compared to that of other medications that are currently available. These studies have shown that buprenorphine treatment:</p> <ul style="list-style-type: none"> <li>• Is more effective than placebo; and</li> <li>• Has similar effectiveness to moderate doses of methadone and levo-alpha-acetyl-methadol or LAAM.</li> </ul>
<p style="text-align: center;"><b>Development of Tablet Formulations of Buprenorphine</b></p> <ul style="list-style-type: none"> <li>• Buprenorphine is marketed for opioid treatment under the trade names of Subutex® (buprenorphine) and Suboxone® (buprenorphine/naloxone)</li> <li>• Over 25 years of research</li> <li>• Over 5,000 patients exposed during clinical trials</li> <li>• Proven safe and effective for the treatment of opioid addiction</li> </ul> 	<p><b>Slide 21: Development of Tablet Formulations of Buprenorphine</b></p> <p>Subutex® = a sublingual tablet containing buprenorphine hydrochloride only</p> <p>Suboxone® = a sublingual tablet containing both buprenorphine hydrochloride and naloxone hydrochloride in a 4:1 ratio</p> <p><b>Suboxone®</b> is the focus of U.S. marketing efforts, even though both formulations are available in the U.S.</p> <p>These medications have a tremendous amount of research behind them to show that they are both safe and effective in the treatment of opioid addiction.</p>
<p style="text-align: center;"><b>Buprenorphine Research Outcomes</b></p> <ul style="list-style-type: none"> <li>• Buprenorphine is as effective as moderate doses of methadone.</li> <li>• Buprenorphine is as effective as moderate doses of LAAM.</li> <li>• Buprenorphine's partial agonist effects make it mildly reinforcing, encouraging medication compliance.</li> <li>• After a year of buprenorphine plus counseling, 75% of patients retained in treatment compared to 0% in a placebo-plus-counseling condition.</li> </ul>	<p><b>Slide 22: Buprenorphine Research Outcomes</b></p> <p>Clinical trials have established the effectiveness of buprenorphine for the treatment of opioid addiction. The clinical studies have shown the following about buprenorphine (for references, see slide 20):</p> <p>Bullet #1: Patients on buprenorphine did as well as patients on a moderate dose of methadone (60mg).</p> <p>Bullet #2: Patients on buprenorphine did as well as patients on a moderate dose of LAAM (70mg/70mg/85mg on a Monday/Wednesday/Friday schedule).</p> <p>Bullet #3: Patients found that taking buprenorphine was a pleasant experience, which encouraged them to be compliant.</p> <p>Bullet #4: When compared to placebo-plus-counseling, 3/4 of the patients receiving buprenorphine and counseling were still in treatment after one year. None of the placebo patients were retained.</p>

<p><b>Opioid Partial Agonists</b></p> <ul style="list-style-type: none"> <li>Buprenorphine – Buprenex®, Suboxone®, Subutex®</li> <li>Pentazocine - Talwin®</li> </ul>	<p><b>Slide 23: Opioid Partial Agonists</b></p> <p>Buprenex® is the injectable formulation of buprenorphine approved and marketed for the treatment of pain; it <b>IS NOT</b> approved for the treatment of opioid addiction.</p> <p>Suboxone® is the buprenorphine/naloxone combination tablet and Subutex® is the buprenorphine only tablet. Only these two tablet formulations are approved for the treatment of opioid addiction.</p> <p>Pentazocine (Talwin) is marketed for pain; it <b>IS NOT</b> approved for the treatment of opioid addiction.</p> <p><i>It may be worth noting that buprenorphine is the only medication with FDA approval that is not schedule 2 (methadone). And that only Suboxone and Subutex are approved. Buprenex is not.</i></p>
<p><b>Buprenorphine/Naloxone Combination and Buprenorphine Alone</b></p> 	<p><b>Slide 24: Buprenorphine/Naloxone combination and Buprenorphine Alone</b></p> <p>This is what the two sublingual buprenorphine tablets look like. You will notice that the tablets look different. This is because they are different doses (2 mg versus 8 mg)</p>
<p><b>What is the Ratio of Buprenorphine to Naloxone in the Combination Tablet?</b></p> <ul style="list-style-type: none"> <li>Each tablet contains buprenorphine and naloxone in a 4:1 ratio <ul style="list-style-type: none"> <li>Each 8 mg tablet contains 2 mg of naloxone</li> <li>Each 2 mg tablet contains 0.5 mg of naloxone</li> </ul> </li> <li>Ratio was deemed optimal in clinical studies <ul style="list-style-type: none"> <li>Preserves buprenorphine's therapeutic effects while taking as intended orally</li> <li>Stimulates opioid effects occur if injected by some physically dependent persons to discourage abuse</li> </ul> </li> </ul>	<p><b>Slide 25: What is the Ratio of Buprenorphine to Naloxone in the Combination Tablet</b></p> <p>The combination includes buprenorphine and naloxone in a ratio of 4:1. This ratio was found to maintain the clinical effects when taken sublingually as intended, BUT cause sufficient discomfort if injected by a physically dependent person (to discourage them from doing so).</p>
<p><b>Advantages of Buprenorphine/Naloxone</b></p> <ul style="list-style-type: none"> <li>Discourages IV use</li> <li>Diminishes diversion</li> </ul>	<p><b>Slide 26: Advantages of Buprenorphine/Naloxone</b></p> <p>This formulation has several advantages:</p> <ul style="list-style-type: none"> <li>It discourages injection use because, when injected, the naloxone in the product will lead to withdrawal, whereas when taken sublingually as prescribed, it will not have that effect.</li> <li>Because of the above point, the combination tablet lowers the likelihood that the medication will be diverted.</li> </ul>

### 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 ≈ 2:1

Naloxone ≈ 15:1

SOURCE: PAIN 2011, 2669.

### Slide 27: Why Combining Buprenorphine and Naloxone Sublingually Works

Digestive juices would kill buprenorphine's effects if you were to swallow it. By administering it sublingually, the medication dissolves under the tongue and is absorbed directly into the blood stream. Buprenorphine and naloxone have very different absorption rates when taken this way.

When taken under the tongue, the person receives approximately 40-60% of the buprenorphine available, but only 10% of the naloxone.

However, when you look at the relative potency comparing sublingual administration to injection, buprenorphine is approximately twice as strong when injected as when taken sublingually. Naloxone, on the other hand, is 15 times more effective by injection.

This means that when taken by injection, the naloxone is the stronger medication and the antagonist effects dominate.

### 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

### Slide 28: Buprenorphine/Naloxone

The effect of the combination tablet is virtually identical to the buprenorphine-only product when taken sublingually.

Both formulations demonstrate the ceiling effect at higher doses.

Both formulations prevent the intoxicating effects if someone decides to also use another opioid.

They are long-acting because of the high receptor affinity.

### Clonidine

- Clonidine - Catapres®
- 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

### Slide 29: Clonidine

Clonidine (Catapres) has gained widespread recognition and acceptance for its usefulness as an agent for symptom suppression of opioid withdrawal.

Clonidine may be used in inpatient and outpatient settings; however, it is most effective when used in an inpatient setting as side effects can be monitored more closely.

It is a centrally acting alpha 2-adrenergic agonist that suppresses activity in the locus ceruleus.

Clonidine partially suppresses peripheral symptoms of opiate withdrawal (e.g., nausea, vomiting, sweating, diarrhea) by decreasing autonomic nervous system activity.

It is also used to treat hypertension.

Clonidine **does not** have an FDA indication for treatment of opioid dependence. However, once a medication has been approved for marketing for a certain use, experience may show that it is also useful for other medical problems. Other off-label uses of clonidine include the following medical conditions:

- Migraine headache
- Symptoms associated with menopause or menstrual discomfort
- Symptoms of withdrawal associated with alcohol, nicotine, or narcotics
- Gilles de la Tourette's syndrome

Off label use is usually based on anecdotal case reports and/or small, uncontrolled studies that indicate efficacy in a specific population. Generally there are not clinical trials to support it.

One of the difficulties in using a medication off label, therefore, is that there is little or no information from clinical trials relating to proper dosage, precautions, or side effects for these off-label uses. The treating physician must use clinical experience to address these issues.

### 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.)

### Slide 30: Why Use Clonidine

Clonidine has some practical advantages over methadone for treating narcotic withdrawal. These include:

- It is not a scheduled medication.
- The use of opiates can be discontinued immediately in preparation for naltrexone induction or admission to a drug-free treatment program (e.g., a therapeutic community).
- Alleviates autonomic mediated signs and symptoms.
- Currently accepted medication for treating opioid withdrawal.
- No special license needed.

However, it is not effective at alleviating subjective effects of opiate withdrawal (e.g., general body aches, abdominal cramps, cravings, etc.). Because of side effects (particularly hypotension), it requires careful dose titration. It is also less effective especially with moderate to severe withdrawal consequently the attrition rate among patients can be very high.

### Contraindication for Use of Clonidine

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

### Slide 31: Contraindications for Use of Clonidine

Contraindications for use of clonidine include: hypertension, hypotension, pregnancy, liver damage, history of auditory hallucinations, delirium, recent myocardial infarction, chronic renal failure, history of fainting or dizziness on rising.

What are the safety issues of clonidine vs. buprenorphine – especially in an outpatient setting (if the medication is not used as indicated)?

If the medication is not used as indicated, Clonidine will add to the effects of alcohol and other central nervous system (CNS) depressants (medicines that slow down the nervous system, possibly causing drowsiness). Some examples of CNS depressants are antihistamines or medicine for hay fever, other allergies, or colds; sedatives, tranquilizers, or sleeping medicine; prescription pain medicine or narcotics; barbiturates; medicine for seizures; muscle relaxants; or anesthetics, including some dental anesthetics.

It may also cause some people to become drowsy or less alert than they are normally.

Dizziness, lightheadedness, or fainting may occur, especially when you get up from a lying or sitting position. This is more likely to occur if you drink alcohol, stand for long periods of time, exercise, or if the weather is hot.



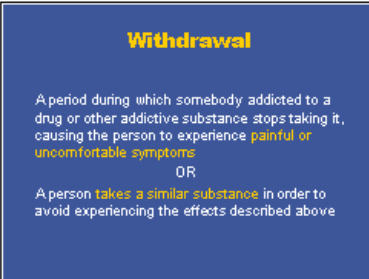
**Slide 32: Medically Assisted Withdrawal (a.k.a. Dose Tapering; a.k.a. Detoxification)**

The data from the study clearly indicates that buprenorphine was more effective than clonidine (a standard treatment) in this 13-day taper. Before we look at the specifics of how to implement this taper, let's talk about opioid withdrawal and what patients experience when going through it.

Opiate withdrawal syndrome, although not life-threatening, is a major obstacle in the treatment of opiate dependence (Mattick & Hall, 1996). Detoxification from opiate dependence most often involves the administration of an opiate agonist (e.g., methadone) or the nonopiate clonidine (Fishbain, Rosamoff & Cutler, 1993; Valmana, 1999).

Withdrawing from the opioids (commonly called detoxification) is often is the first step in the treatment of opioid dependence. It is the start of a continuum of care that needs to be carefully planned and followed.

Not all patients are appropriate for withdrawal from the medications. Unstable living situations, multiple relapses, previous failed detoxification attempts, or lack of desire to withdraw from opioids, may indicate that maintenance is a better treatment option.



**Slide 33: Withdrawal**

**Withdrawal syndrome:** the predictable constellation of signs and symptoms following abrupt discontinuation of, or rapid decrease in, intake of a substance that has been used consistently for a period of time.

**Detoxification:** implies a clearing of toxins (Alling, 1992). However, for individuals with physiological substance dependence, detoxification is defined as the management of the withdrawal syndrome (Kasser et al., 2004) to help the person move to an opioid-free state. In this training we will refer to this as an **opioid taper**.

### 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

### Slide 34: Withdrawal Syndrome

Once the body becomes accustomed to a drug being on board, it may react if the drug is removed. The intensity of the withdrawal symptoms will depend on the level of use (e.g., dose and type of opioid) and the frequency and duration of use (chronicity).

Withdrawal symptoms are basically a rebound effect; those functions that have been depressed or altered by the opioid suddenly emerge again. Withdrawal symptoms are often the opposite of symptoms seen when actively using the opioid (e.g., people get constipated when taking opioids and have diarrhea when withdrawing).

Length of withdrawal depends upon the half-life. Opioids with short half-lives (e.g., heroin) have acute withdrawal symptoms that peak at 3-4 days and then subside by days 3-7. Opioids with longer half-lives have longer acute withdrawal periods.

Regardless of the length of the acute withdrawal, there are protracted withdrawal symptoms (e.g., aches and pains, general malaise) that persist for weeks or months after use ceases.

### 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

SOURCE: Principles of Drug Dependence: Treatment of Prescription-Abuse (Gale, N Ed., 2006).

### Slide 35: Medically- Assisted Withdrawal

The individual is systematically withdrawn from addicting drugs. Medications (e.g., methadone, buprenorphine, clonidine) are used to alleviate withdrawal symptoms while the person gradually returns to an opioid free state.

It can be done successfully in inpatient or outpatient settings, but the treatment plan should be carefully developed to ensure adequate structure and support.

Generally a medical provider supervises the withdrawal to monitor medical safety and administer medications to relieve discomfort.

Generally this approach is not sufficient by itself to transition someone to maintaining an ongoing opioid-free life. Longer-term treatment that helps the person to develop new behaviors and strategies for coping is critical.

Patients who are not successful in withdrawing or who choose not to withdraw from opioids should be considered for treatment with medications as part of the treatment plan (either short- or long-term).

### 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

### Slide 36: Goals of Medically-Assisted Withdrawal

Medically- assisted withdrawal can be said to have three immediate goals: (1) to provide a safe withdrawal from alcohol or other drug(s) of dependence and enable the patient to become free of non-prescribed medications; (2) to provide a withdrawal that is humane and that protects the patient's dignity; and (3) to prepare the patient for ongoing treatment of his or her dependence (Wesson, 1995):

- (1) To assist patients transition off of opioids so that they are no longer physically dependent. Psychosocial treatment is a critical component of this (and all treatments) to help them avoid relapse.

Withdrawal from opioids produces severe discomfort but generally is not life threatening. It may, however, present a danger to those experiencing other medical conditions (i.e., advanced HIV disease, advanced age, coronary artery disease). It is important to note when medically-assisted withdrawal is conducted in an outpatient setting, patients experiencing withdrawal symptoms may self-medicate with alcohol or other drugs which may result in an overdose.

- (2) To provide a withdrawal that is humane and thus protects the patient's dignity. A caring staff, a supportive environment, sensitivity to cultural issues, confidentiality, and the selection of appropriate ancillary medication all are important to providing humane withdrawal. However, staff must be firm as well as sympathetic and have experience in dealing with difficult behaviors that often accompany medically- assisted withdrawal (Wesson, 1995).

- (3) To prepare the patient for ongoing treatment of his or her dependence on alcohol or other drugs. During withdrawal, patients may form therapeutic relationships with treatment staff or other patients, and may become aware of alternatives to an alcohol- or drug-using lifestyle. It is an opportunity to offer patients information and to motivate them for longer-term treatment (Wesson, 1995).

**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

**Slide 37: Principles of Medically-Assisted Withdrawal**

Some withdrawal procedures are specific to particular drugs of dependence, while others are based on general principles of treatment and are not drug-specific.

Initial medical assessment should include evaluation of predicted withdrawal severity and medical or psychiatric co-morbidity. Because there is a risk of serious adverse consequences for some patients who undergo withdrawal, an initial assessment should be conducted and include, the amount and duration of a patient's use of alcohol and/or other drugs, the severity of the patient's prior withdrawal experiences, if any (many individuals undergo the withdrawal process more than once), as well as the medical and psychiatric history.

There are two general strategies for pharmacologic management of withdrawal: (1) suppression of withdrawal by a cross-tolerant medication, and (2) decreasing signs and symptoms of withdrawal by alteration of another neuropharmacological process.

Medication assisted withdrawal alone rarely constitutes adequate treatment. Psychological support is extremely important in reducing the patient's distress during the withdrawal process.

The appropriate level of care following withdrawal must be clinically determined, based on the individual needs of the patient. Factors to consider include medical and psychiatric conditions, motivation, relapse potential, and available support system.

**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 period of time (a few days to weeks depending upon the program)
  - Use other medications to treat withdrawal symptoms
- Use clonidine and other non-opioid medications to manage symptoms during withdrawal

**Slide 38: Medically-Assisted Withdrawal**

Medically assisted withdrawal can be successful in either inpatient or outpatient settings. It is important for the multidisciplinary treatment professional to provide supportive wrap-around services to get the patient through this difficult stage.

This is done by transitioning the person onto a long-acting opioid like buprenorphine and then tapering him/her off over a period of time.

Other medications may be helpful if withdrawal symptoms are present to help the person to stay comfortable.

**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.

**Slide 39: Why the Focus on Medically-Assisted Withdrawal (Detoxification)?**

- Bullet #1: Much of the data that has been generated on the use of buprenorphine has focused on its use as a maintenance agent. Less is known about how to use it for opioid withdrawal.
- Bullet #2: More research is critical if we are to understand the best ways of using the medication to assist with patients with withdrawal from opioids.
- Bullet #3: Community Treatment Programs participating in the NIDA Clinical Trials Network (CTN) span the diversity of treatment options available in the field. By studying treatment innovations in this environment a good picture can be achieved of how the treatment will work in the community at large.

**The Research: CTN Protocols 0001 and 0002**

**Slide 40: The Research: CTN Protocols 0001 and 0002**

This package of materials is based on research conducted through the CTN.

For the first studies conducted by the CTN, NIDA chose to compare a standard treatment for helping patients withdraw from opioids (clonidine) to a new treatment (buprenorphine). Two clinical trials were developed and implemented to compare these medications.

**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

**Slide 41: The Two Buprenorphine Naloxone Protocols**

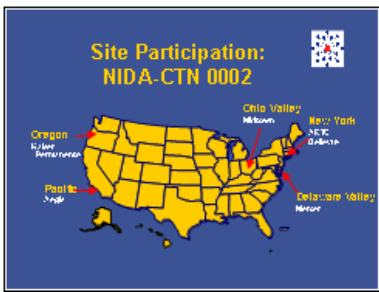
The studies were identical except the type of treatment program in which the program was conducted. The first protocol was conducted in inpatient settings and the second was conducted in outpatient settings.

**Site Participation: NIDA-CTN 0001**

**Slide 42: Site Participation NIDA-CTN 0001**

The studies were conducted in 8 Regional Nodes and 12 Community Treatment Programs

For the inpatient protocol, six sites in five regional nodes across the country participated in the study.



**Slide 43: Site Participation NIDA-CTN 0002**

Six sites in five nodes also participated in the outpatient study.

**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

**Slide 44: NIDA CTN 001/002 Buprenorphine Naloxone Detoxification Protocols**

As information is being gathered to determine whether or not a medication is effective for treatment of a particular problem, the studies are usually blinded. This means that the patient (and usually the researcher) do not know if a particular patient is taking the active medication or a placebo. It is only after the study is completed that the blind is broken and the researcher can evaluate the effect of the medications.

These blinding procedures prevent expectations about the medication from positively or negatively influencing the results.

After efficacy of the medication has been established, researchers may want to explore specific indications or ways of using the medication. These studies are often open-label studies. In open-label studies, patients and researchers both know what they are taking.

Another way that researchers control bias or expectations from influencing the results is through randomization. This means that the person is assigned to their study group by chance. In the current study, participants were randomly assigned to receive either buprenorphine or clonidine.

Community Treatment Programs	
<b>6 Inpatient</b> 2 Therapeutic Communities 1 Free-standing Chemical Dependence Hospital 2 Detox Units with Integrated Addiction and Mental Health Services 1 Long Term Residential	<b>6 Outpatient</b> 4 Opioid Treatment Programs 1 HMO 1 Community Mental Health Center
Usual care approaches: 80% methadone, 20% clonidine	Usual care approaches: methadone in OTPs and clonidine in HMO

**Slide 45: Community Treatment Programs**

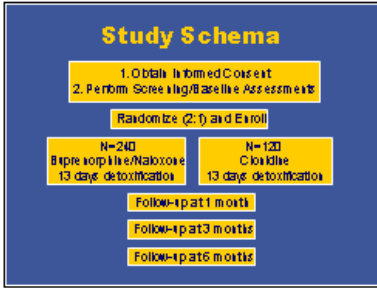
There was considerable variability in several areas in both the inpatient and outpatient programs.

CTP and physicians' experience with opioid users and narcotic treatment medications varied. Nine of the 12 physicians participating were certified by the American Society for Addiction Medicine; all actively treated substance abusers; training backgrounds included addiction psychiatry, internal or family medicine, pediatrics or anesthesiology; professional experience ranged from 1-20 years.

Staffing patterns and experience participating in research also varied. Some had many years of experience participating in research while others never participated.

In the inpatient programs, about half of the programs currently provided detox with methadone and half with clonidine. In outpatient, 4 of the 6 programs were methadone programs and used methadone, the other 2 used clonidine.

This variability in the programs suggests that the results can be interpreted beyond a specific type of program, but the results are probably applicable to a variety of different program types.



**Slide 46: Study Schema**

The goal of CTN 0001 and 0002 was to compare the efficacy of these two medications for short-term opioid withdrawal. The two-week timeframe was decided upon by the investigators. The time frame was long enough to cover the length of time for someone who quit “cold turkey” to be through the acute withdrawal period. This timeframe also met requirements of several agencies’ funding restrictions related to length of stay. Thus this was a schedule that could be implemented in programs if the research proved its efficacy.

A standard taper schedule was used so that all patients received buprenorphine or clonidine in accordance to a predetermined schedule on each day of the taper. Ancillary meds were available to treat breakthrough withdrawal symptoms.

This slide shows the order of procedures for participants in the study. After obtaining informed consent, baseline screening and assessments were conducted. Participants were then randomized in a two-to-one ratio to buprenorphine or clonidine. Participants received medication and evaluation for 13 days and then were followed up at one, three and six 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.

### Slide 47: Primary Efficacy Endpoint

The researchers conducting this study believed that patients receiving buprenorphine would have a better treatment response than those receiving clonidine. To determine if this was true they needed to define a way to measure treatment response.

A positive treatment response was defined as being present on the final day of the taper (day 13, the last day to receive medication OR day 14, the first day off of the medication), AND providing an opioid free urine sample (meaning no illicit opioids had been used).

It is **important to note** that this study addressed only the process of tapering patients off of opioids so that at the end of the taper they were opioid free. Ongoing care and follow-up were not addressed in the result of this trial, but are thought to be important considerations for patients who receive this taper in real-world settings.



### Slide 48: So, what did we find?

The results from this study were pretty dramatic. Let's look at the inpatient study first.

### Demographics 0001 (Inpatient)

	Bup/Nx	Clonidine	Total
<b>Sex (n, %)</b>			
Male	81	68	80
Female	28	42	40
<b>Race (n, %)</b>			
White	68	68	68
Black	18	18	18
Hispanic	12	17	18
Other	8	5	8
<b>Age (n, Years, Mean (SD))</b>	36.8	37.4	-
<b>Employed (n, %)</b>	-	-	88
<b>Mean Education in Years (SD)</b>	-	-	12.3 (1.7)
<b>Mean Years of Heroin Use (SD)</b>	-	-	8.8 (8.1)

### Slide 49: Demographics 0001 (Inpatient)

Demographics were similar across the 2 groups. They were:

- Predominantly male
- Predominantly white, but with representation from other ethnic minority groups.
- Participants were in their mid-30s.
- 2/3 were employed.
- They had been using heroin for about 6½ years at the time they began the study.

### Present and Opioid Negative 0001 (Inpatient)

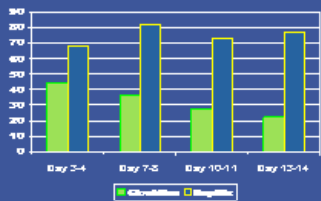
Present and opioid neg	Bup/Nx (N)	%	Clonidine (N)	%
#	77		38	
Day 3 or 4	62	87.6	18	44.4
Day 7 or 8	65	81.3	12	38.1
Day 10 or 11	68	72.7	10	27.3
Day 13 or 14	69	78.8	5	22.2

### Slide 50: Present and Opioid Negative 0001 (Inpatient)

Data collection visits were conducted according to this schedule (Day 3-4, 7-8, 10-11, and 13-14). Urine samples were collected at each visit. Collection was monitored using temperature, but was not directly observed. The data presented in the slides at this point pertains specifically to opiate-free urines.

Among the participants in the inpatient study, 3/4 were present on at the end of the taper AND provided an opioid negative urine sample. In the clonidine group, only 22% were present and opioid negative at the end of the taper.

**Present and Opioid Negative 0001 (Inpatient)**



**Slide 51: Present and Opioid Negative 0001 (Inpatient)**

This slide shows the same information graphically.

**Demographics 0002 (Outpatient)**

	Bup (N)	Clonidine (N)	Total
<b>Sex (N, %)</b>			
Male	72	89	72
Female	27	31	28
<b>Race (N, %)</b>			
White	40	40	40
Black	38	28	37
Hispanic	21	18	20
Other	8	8	8
<b>Age in Years: Mean (SD)</b>	33.8	40.0	-
<b>Employed (%)</b>	-	-	68.8
<b>Mean Education in Years (SD)</b>	-	-	12.4 (2.1)
<b>Mean Year of Heroin Use (SD)</b>	-	-	8.4 (8.8)

**Slide 52: Demographics 0002 (Outpatient)**

In the outpatient study, there was a higher percentage of male participants than in the inpatient study (72% vs. 60%). The proportion of minority participants was higher in this study as well (60% vs. 44%). The participants were slightly older (39 vs. 36 years old) and had been using heroin longer the inpatient study (9.4 years vs. 6.6 years).

**Present and Opioid Negative 0002 (Outpatient)**

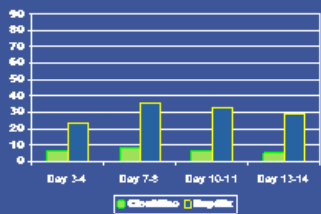
Present and opioid neg	Bup (N)	%	Clonidine (N)	%
<b>N</b>	167		74	
Day 3 or 4	37	22.2	6	8.0
Day 7 or 8	68	40.7	8	10.7
Day 10 or 11	62	37.1	6	8.0
Day 13 or 14	48	28.6	4	5.3

**Slide 53: Present and Opioid Negative 0002 (Outpatient)**

Overall the numbers present and opioid negative at the end of the taper were lower than in the inpatient study. The researchers expected this difference given the fact that in the inpatient settings, clients were contained within the treatment environment. In outpatient settings, participants are still living in their environments and therefore come in contact with more factors that can pull them away from treatment. In spite of the lower numbers, however, the results are still dramatic.

At the end of the taper nearly 1 in 3 participants receiving buprenorphine were present and provided an opioid negative urine sample. In the clonidine group, only 1 in 20 were present and opioid free.

**Present and Opioid Negative 0002 (Outpatient)**



**Slide 54: Present and Opioid Negative 0002 (Outpatient)**

Again, this slide shows the same information graphically.

### 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 : Bup/Nx = **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

### Slide 55: NNT: Number Needed to Treat

Another way of looking at these data is to look at the number of patients that need to be treated in order to get one successful outcome (again defines as a positive treatment response—present and opioid negative).

If you take the total number of participants receiving a treatment and divide by the number successfully completing the treatment, you get the number of patients you need to treat (on average) for one successful treatment.

Using this methodology, in the inpatient study you need to treat 1.3 patients with buprenorphine to get one successful outcome versus 4.5 when treatment with clonidine. Stated another way, you would need to treat 3.4 times more people with clonidine than with buprenorphine to get a positive treatment response.

In the outpatient study you need to treat more people to get a positive result. With buprenorphine, you need to treat 3.4 patients to get one successful outcome. However, with clonidine you need to treat 18.5 means that you would need to treat 5.4 times more people with clonidine than with buprenorphine to get a positive treatment response.

#### **Ask participants:**

What are the implications of this for deciding how to treat patients?

*(Possible answers/discussion points: Treating with buprenorphine more likely to lead to a successful taper; patient experience is better with buprenorphine; if an individual patient is selecting a treatment, they would want to choose the one with the higher likelihood of success).*

### Protocol

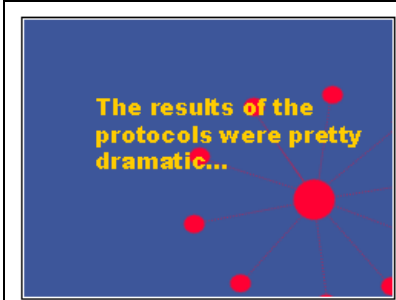
Designed to examine the use of Suboxone® (buprenorphine/naloxone) versus the use of clonidine in a short-term opioid withdrawal, in inpatient and outpatient settings

### Slide 56: Protocol

This protocol was 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.

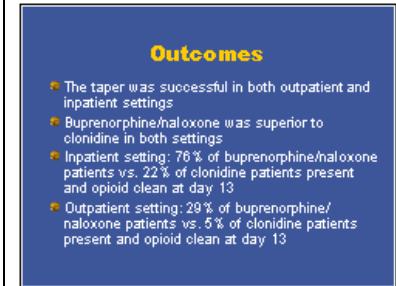
The three main objectives of the program were:

- Patient compliance and treatment retention
- Opioid abstinence should be achieved
- Minimal abstinence symptomology should result from the dose reduction schedule in order to minimize the risk for relapse.



**Slide 57: The Results of the Protocol Were Pretty Dramatic**

In summary, the result of these protocol support the use of buprenorphine for this 13-day taper schedule.



**Slide 58: Outcomes**

A 13-day taper, utilizing a prescribed schedule demonstrated the following results:

- The taper was successful in both outpatient and inpatient settings
- Buprenorphine was superior to clonidine in both settings
- The percent of those present and opiate clean at day 13 was higher among the inpatient buprenorphine patients (76%) than among the inpatient clonidine patients (22%).
- The percent of those present and opiate clean at day 13 was higher among the outpatient buprenorphine patients (29%) than among the outpatient clonidine patients (5%).
- Generalizability is supported by: representative sampling of minority populations and the sample population was geographically representative.
- The sample population given Suboxone® had lower withdrawal symptoms



**Slide 59: So If I Want to Do This, What Steps Do I Take**

*Transition slide: read text*



**Slide 60: First, the Patient must be Screened for Appropriateness for Buprenorphine Treatment**

Most patients can be considered for treatment with buprenorphine provided they are opioid dependent and interested in medication-assisted detoxification.

### 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

### Slide 61: Screening Assessment Used in the CTN Protocols

Prior to participation in the protocol a screening assessment was completed and included:

- Medical history and history of prior medication use
- Psychiatric evaluation (ASI Lite)
- Completion of the DSM-IV checklist for substance dependence
- HIV risk assessment
- Hepatitis B and C Serology

It is important to note that the effect of hepatic impairment on buprenorphine and naloxone is unknown. Since both drugs are extensively metabolized, the plasma levels will be expected to be higher in patients with moderate and severe hepatic impairment. In patients with hepatic impairment dosage should be adjusted and patients observed for symptoms of precipitated opioid withdrawal.

An HIV risk assessment was included for several reasons - this particular assessment is used in all CTN studies; individuals who are injecting drugs are at a higher risk for HIV infection and Hepatitis C, which may complicate addiction treatment.

### Safety Assessment Used in the CTN Protocols

- Physical examination
- Vital signs
- Blood chemistry
- Hematology
- Urinalysis
- 12 Lead electrocardiograph (ECG)
- Pregnancy test

### Slide 62: Safety Assessment Used in the CTN Protocols

A safety assessment was also completed on each patient and included:

- Physical examination
- Vital signs
- Blood chemistry
- Hematology
- Urinalysis
- 12 Lead electrocardiograph (ECG)
- Pregnancy test

At the time of the development of this module, there are no adequate and well-controlled studies of Suboxone® in pregnant women. However clinical studies are currently underway and showing promising results.

Of special note: use of high doses of sublingual buprenorphine in pregnant women has showed that buprenorphine passes into the mother's milk. Breast-feeding is therefore not advised in mothers treated with Suboxone®.

Numerous studies have demonstrated that when taken as recommended, buprenorphine has been well tolerated and that there are few significant side effects.

The question has been asked, "Do you really need to do a physical to give someone buprenorphine?"

In the CTN studies a physical exam was conducted as part of the safety assessment for participation in the study. The protocol was overly stringent with regard to exclusion criteria because a chance a patient could be randomized onto clonidine, which as previously discussed have several contraindications.

It may be good to have the baseline assessment to determine their general health and identify other issues that may need treatment (hooks them into the medical system, even if it is not completely necessary to start someone on buprenorphine). As with all medical decisions, the physician should use his/her best medical judgment to determine if and when this should occur.

**Once you determine that buprenorphine is the best treatment...**

**...the next step is induction**

**Slide 63: Once you determine that buprenorphine is the best treatment...the next step is induction**

Starting the patient on the medication is pretty straight forward, but must be planned in order to ensure a smooth transition onto buprenorphine. If buprenorphine is not given appropriately, an opioid dependent patient can experience withdrawal symptoms.

**Transferring Patients Onto Buprenorphine: 3 Ways Significant Withdrawal Could Occur**

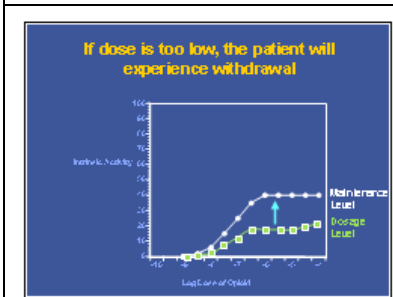
Does too low?

Insufficient agonist effect

**Slide 64: Transferring Patients Onto Buprenorphine: 3 Way Significant Withdrawal Could Occur**

There are three ways that a patient can experience withdrawal symptoms.

First, if an insufficient dose of buprenorphine is given, the person may experience withdrawal from being under medicated.



**Slide 65: If dose is too low, the patient will experience withdrawal**

This graph represents how under-medication can result in withdrawal symptoms. If the patient is given a low level of medication (represented by the green line), but needs higher level in order to not feel sick (represented by the white line), the person will feel sick unless the dosage is increased to bring them up to this level.

**Transferring Patients Onto Buprenorphine: 3 Ways Significant Withdrawal Could Occur**

Does too low?

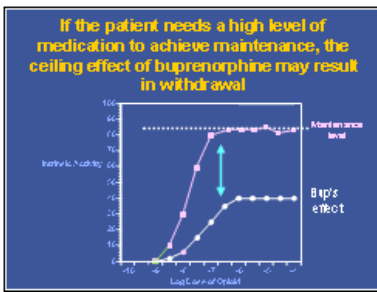
Insufficient agonist effect

Not full agonist

May not fully substitute

**Slide 66: Transferring Patients Onto Buprenorphine: 3 Way Significant Withdrawal Could Occur**

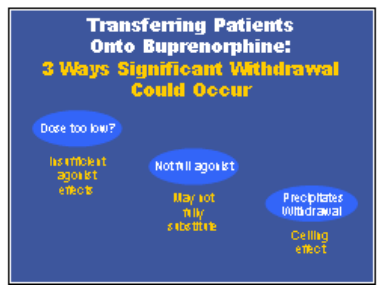
A second way that a person can experience withdrawal has to do with the properties of buprenorphine itself—the ceiling effect.



**Slide 67: If the patient needs a high level of medication to achieve maintenance, the ceiling effect of buprenorphine may result in withdrawal**

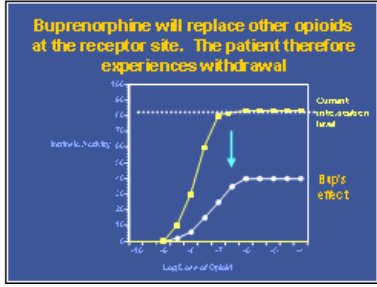
As described before, as the dose of buprenorphine increases, the agonist effects level off. For someone who is dependent of very high doses of opioids, they may need an effect greater than can be achieved with buprenorphine in order to no feel sick.

In this case, treatment would need to be provided using a full agonist (e.g. methadone) or the person would need to taper down their dose to a lower level before switching to buprenorphine. This can be done in a structure opioid treatment program, but should not be attempted with someone using illicit opioids.



**Slide 68: Transferring Patients Onto Buprenorphine: 3 Way Significant Withdrawal Could Occur**

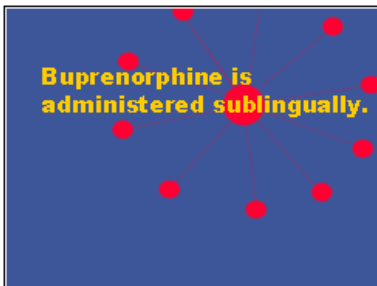
Finally, there is precipitated withdrawal. This also has to do with the ceiling effect and receptor affinity.



**Slide 69: Buprenorphine will replace other opioids at the receptor site. The patient therefore experiences withdrawal**

If the person is currently intoxicated on an opioid, the opioid receptors are filled with this drug. Buprenorphine, however, has a stronger affinity for the receptors than illicit opioids and will replace these opioids on the receptor. Due to the ceiling effect, the experience of the patient will be that the level of opioids in the system has suddenly decreased. This will be experienced as withdrawal.

In order to avoid this, buprenorphine should only be administered once the person is in mild withdrawal. This will result in a reduction of the withdrawal symptoms and the experience of feeling better/normal.



**Slide 70: Buprenorphine is administered sublingually.**

The sublingual tablet should be held under the tongue until dissolved, which can take 2 to 10 minutes.

For this protocol, dissolution was monitored by personnel at the clinic by looking under the tongue to ensure that the tablet was gone to ensure that all of the medication had been taken.

**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.



**Slide 71: What will the tablets look like? How will they taste?**

The Suboxone tablets were the ones chosen for these protocols since the pharmacology of the buprenorphine/naloxone combination is the same as for buprenorphine alone and the combination reduces the chance of diversion as described previously.

The tablets are orange and have a citrus flavor to mask the bitter taste experienced by some people.

**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

**Slide 72: Five Steps to Starting Bup/Nx**

There are five recommended steps for initiation treatment with buprenorphine.

First, it is recommended that the patient be in mild withdrawal prior to taking their first dose of buprenorphine. This means that they must abstain from use of illicit opioids prior to induction. For short acting opioids (e.g., heroin) an interval of about 8 hours is recommended. For longer acting opioids, the interval will need to be increased to 24 or even 48 hours.

Mild withdrawal can be evaluated based on clinical signs. Using a structured instruments such as the Clinical Opioid Withdrawal Scale (COWS), developed by Wesson and Ling (2003), can provide a way of rating these clinical signs to determine opioid withdrawal.

Clinical Opiate Withdrawal Scale (COWS): This is an 11-item interviewer administered questionnaire designed to provide a description of signs and symptoms of opiate withdrawal that can be observed directly in the patient (e.g., sweating, runny nose, etc.). Provides for accurate objectification of symptoms, allowing for appropriate prescribing of medication

**The dosing schedule**



**Slide 73: The dosing schedule**

The dosing schedule for this taper was uniform for everyone. This was necessary for research purposes. Additionally, it has the benefit of ensuring the people are brought onto buprenorphine as quickly as possible and then tapered of over as long as possible.

The specific dosing schedule is a follows:

### Day 1 Dose Induction

Bup-Nx DOSE	Day 1	Day 2	Day 3
	4/1 + 4/1	8/2	16/4

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

### Slide 74: Day 1 Dose Induction

During the research study, participants were asked to come to the clinic daily for medication, assessments and monitoring of withdrawal symptoms to determine the need for ancillary medications.

The initial dose was always given to the patient in the clinic. They were assessed to be in mild withdrawal using the COWS and then were given 4 mg of buprenorphine sublingually. They were observed and a nurse checked under their tongue to make sure the medication had completely dissolved.

Patients were instructed to wait in the clinic for two hours to ensure that they were tolerating the medication and to determine if an additional 4 mg of buprenorphine was indicated. The majority of patients receive both 4 mg doses.

On the second day of the study, the dose was 8 mg. This dose was given in a single administration rather than split as in day 1. On the third day, the dose increased again to 16 mg. After day 3 the tapering of the medication began with ever decreasing dosages.

### BUP-NX Taper Schedule

Day	Bup/Nx Dose (mg of bup)
1	4 (+ 4 if needed)
2	8
3	16
4	14
5	12
6	10
7	8
8-9	6
10-11	4
12-13	2

### Slide 75: BUP-NX Taper Schedule

This list indicates the dosages for each day of the taper. Using this schedule, day 14 would be the first day that the patient is opioid free.

Standard dosing was used throughout the protocol (the doses on the schedule were the doses administered).

Patients were retained in the trial better in the buprenorphine group than in the clonidine group. In both groups, the majority of the dropouts came between day 3 and 4. This is not surprising given that this is when the withdrawal symptoms would be most severe.

The study was successful, but will it work for everyone?

### Slide 76: The study was successful, but will it work for everyone?

Any time you are evaluating research, it is important to look at the results carefully to determine how far the results can be generalized. The reality is, we can never really answer this question definitively, but we can generate some understanding of who this might work for by looking at who was included in the study and who was excluded.

### 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  $\geq$  100mm 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

### Slide 77: Inclusion Criteria for the CTN Protocols

The inclusion and exclusion criteria for participation in this trial were very stringent. This is due in part to the fact that the comparison group received clonidine, which, as we have already discussed, has significant contraindications. We cannot determine from this study how the results may change if these criteria were less stringent.

- Both buprenorphine and clonidine are labeled as Category C for pregnancy.

This means that **EITHER** animal studies have revealed adverse effects on the fetus and there are no controlled studies in women **OR** studies in women and animals are not available. Drugs should be given only if the potential benefit justifies the potential risk to the fetus.

Additionally, buprenorphine is labeled as “possible unsafe” during lactation and clonidine is labeled as “safety unknown.”

For these reasons, pregnant and lactating women were excluded from the trial.

- In order to be appropriate for a medically-assisted opioid taper, the person must be dependent on opioids and need assistance in getting off of them.
- The blood pressure requirements were included primarily as a safety concern for patients receiving clonidine.
- The person must be in good enough health to participate safely in the trial and, in instances where they are receiving treatment, be willing to coordinate their care to ensure that their wellbeing is not compromised.

**Inclusion Criteria for the CTN Protocols (continued)**

- 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

**Slide 78: Inclusion Criteria for the CTN Protocols**

- All participants in a research trial must be able to provide a valid informed consent.

This means that the participant has had the nature of the study explained to the including the details about the study, such as its purpose, duration, required procedures, and key contacts, risks and potential benefits. The participant then decides whether or not participate in the study.

Minors cannot legally sign consent, so a parent or legal guardian would need to consent for them.

- Due to the concerns about pregnancy with these medications, use of an acceptable form of birth control was required female participants.

**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

**Slide 79: Exclusion Criteria for the CTN Protocols**

Clients were excluded from participation in the trial if they met any of these exclusion criteria:

- If the person was found to have a significant medical disease. These were conditions they were potentially thought to compromise the safety of the participant. Clinically a physician may still decide to treat such patients with either of the medications being investigated in this trial, but it is unclear from these results what impact that will have on outcome.
- If ECG anomalies were seen a physician would be asked to evaluate it to determine if the finding was clinical significant.
- Known allergy or sensitivity to a medication would indicate that it is not an appropriate source of treatment. In the case of a research study, where they physician and the patient get not choice as to which medication they will receive due to random assignment, sensitivity to any of the medications being studied would therefore exclude participation.
- There are many medications known to negatively interact with clonidine. If the person was receiving any one of these, they were excluded from participation, again because random assignment may place them in the clonidine group, which would compromise their safety.
- Severe psychiatric issues or suicidal risk would exclude as the person needs to be stabilized urgently and then treatment of other conditions considered.

### 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

### Slide 80: Exclusion Criteria for the CTN Protocols

- Caution is advised for use of CNS depressants, especially benzodiazepines, due to increase risk of respiratory depression when combined with either buprenorphine or clonidine. Evaluation of level of use of these substances and/or need for medical detoxification is important in evaluating the safety for use with buprenorphine or clonidine.
- Due to potential confounding of results, recent participation in another investigational trial excluded participation in this trial.
- Regular use of these long-acting opioids could potentially confound the results of this trial. Therefore, participants were excluded if they had been using them in the past month for maintenance or withdrawal from opioids. Additionally, participants were required to provide a methadone negative urine sample prior to induction with the study medications.
- Pregnancy and lactating concerns have already been discussed above.

### Ancillary Medications for Treatment of Withdrawal Symptoms

### Slide 81: 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

### Slide 82: Ancillary Medications

The use of ancillary medication during opioid withdrawal is fairly common, especially when using non-narcotic agents such as clonidine.

Dispensing of ancillary medications was at the physician's discretion in accordance with clinical need to assist with the management of withdrawal signs and symptoms.

However, the choice of which medication could be given was 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.

**Slide 83: List of Ancillary Medications**

Following is a list of the ancillary medications that were used for this protocol.

These medications were selected by consensus of the physicians participating in the trial. Medications were chosen based on their efficacy in treatment a specific withdrawal symptom and to provide the physicians with choice as to how to treat the symptoms. Once selected for the protocol, these medications were standardized and were the ONLY choices available for use.

It is not clear what effect it will have on the course of treatment or the outcomes if different medications are used.

Physicians were not required to dispense each ancillary medication, but rather to provide them according to their personal preference, practice and patient’s clinical need. However, only one type of ancillary medication was administered for any given symptom on a given day. A physician could choose to try different medications across days.

For outpatient programs, participants received the medication in a childproof bottle for self-administration at home in accordance with the printed instructions on the bottle.

At the start of the detoxification, patients were given instructions regarding the use of the medication. Refills were made available to all participants during each scheduled clinic visit.

**Ancillary Medications Used in the CTN Protocols**

Bone Pain and Arthralgias

- Acetaminophen 650 mg q 4-6 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.
- Donnatal 1-2 tablets q 6-8 hrs prn; NTE 8 tablets per 24 hrs.

**Slide 84: Ancillary Medications Used in CTN Protocols**

Following are the withdrawal symptoms and the medications that were available to treat them:

- 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 q 6 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)

**Ancillary Medications  
Used in the CTN Protocols**

Anxiety and Restlessness (use one of the following)

- **Lorazepam (Ativan)** 1-2mg q 6 hrs. prn; NTE 8 mg per 24 hrs.
- **Oxazepam (Serax)** 15-30 mg po q6 hrs. prn; NTE 120mg 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.

**Slide 85: Ancillary Medications Used in CTN Protocols**

Anxiety and Restlessness

- **Lorazepam** (1-2 mg q 6 hrs. prn; NTE 8 mg/24 hrs)
- **Oxazepam** (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** (50 mg, po q 6 hrs. prn; NTE 200 mg per 24 hrs)

Physicians prescribing the medications were aware of the cautions related to over use of benzodiazepines and dosages were selected to be effective for treating anxiety without putting the person at risk. Patients were also evaluated on an ongoing basis for misuse of the medication. Additionally, non-benzodiazepine options were available.

**Ancillary Medications  
Used in the CTN Protocols**

Nausea

- **Trimethobenzamide (Tigan)** 250 mg q8 hrs prn; NTE 750mg 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

**Slide 86: Ancillary Medications Used in CTN Protocols**

Nausea

- **Trimethobenzamide (Tigan)** (250 mg q 8 hors 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** (50mg, 1 to 3 tabs, po qhs prn)
- **Doxepin Hydrochloride** (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

Insomnia	Bone Pain & Arthralgia	Anxiety & Restlessness	Nausea	Diarrhea
62%	54%	52%	55%	25%

- Average of 2.3 withdrawal symptoms were treated

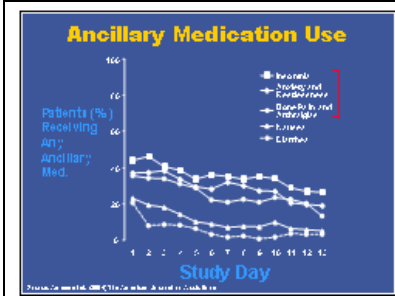
From the results of the CTN studies. Available at: [www.ctn.org](http://www.ctn.org)

**Slide 87: Ancillary Medications Used Among Patients Receiving Buprenorphine**

There were no difference between groups in the rates of using ancillary medications in either the inpatient or the outpatient studies.

Results indicated that about 1 in 5 participants (20%) received no ancillary medications. The other 80% received at least one medication.

The most common symptoms treatment were **insomnia** (most commonly treated with zolpidem tartrate (Ambien) or Trazadon), **bone pain and arthralgia** (most commonly treated with ibuprofen), **anxiety and restlessness** (most commonly treated with lorazepam [Ativan] or oxazepam [Serax]). Only trimethobenzamide [Tigan] was available to treat **nausea**, and **diarrhea** was treated solely using loperamide [Immodium].



**Slide 88: Ancillary Medication Use**

Looking only at the participants receiving buprenorphine, you can see the steady decrease in patients receiving ancillary medications across the course of the study for all types of withdrawal symptoms.



**Slide 89: Adverse Events**

Patients did report additional symptoms or problems during the taper. These are defined in research protocols as adverse events.

- 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.

**Slide 90: 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)

## Slide 91: Adverse Events

A staff nurse or physician/clinician assessed adverse events on a daily basis during the withdrawal process and at the 1-month follow-up visit.

The patient was asked, "How have you been feeling since I saw you last." The type and severity of the adverse effect was recorded.

Assessment instruments used included:

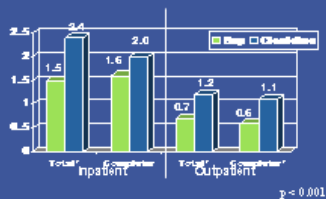
- Clinical Opiate Withdrawal Scale (COWS)
- Adjective Rating Scale for Withdrawal (ARSW)
- Visual Analog Report (VAS)

Clinical Opiate Withdrawal Scale (COWS): This is an 11-item interviewer administered questionnaire designed to provide a description of signs and symptoms of opiate withdrawal that can be observed directly in the patient (e.g., sweating, runny nose, etc.). Provides for accurate objectification of symptoms, allowing for appropriate prescribing of medication (Wesson & Ling, 2003).

Adjective Rating Scale for Withdrawal (ARSW): The ARSW is comprised of 16 signs and symptoms of opioid withdrawal (Bickel et al., 1988a, 1988b; Amass et al., 2000). Patients rate themselves on a scale ranging from 0 (none) to 9 (severe) (maximum cumulative score = 144) on the following items: muscle cramps, depressed or sad, painful joints, excessive yawning, hot or cold flashes, trouble getting to sleep, sick to stomach, irritable, runny nose, poor appetite, weak knees, excessive sneezing, tense and jittery, watery eyes, abdominal cramps, and fitful sleep.

Visual Analog Report (VAS): This scale consist of 100 point lines anchored with "not at all" on one end and "extremely" on the other.

## Number of Adverse Events for Total Sample and Completers



## Slide 92: Adverse Events

Differences were seen across groups in the number of adverse events reported per individual.

In the inpatient study, significant difference were seen in the number of events reported for the total sample but not for those completing the taper.

Differences were seen in both the total samples and completers in the outpatient study.

It is impossible to compare the relative number of adverse events reported in the inpatient versus outpatient groups. It is likely that larger numbers were seen in the inpatient settings simply by virtue of the fact that the were in the facility 24-hours allowing for increased observation unlike in the outpatient settings where participants were only in clinic for study related procedures.

### BUP/NX Safety Profile was Excellent

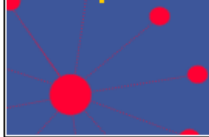
- Eighteen individuals experienced serious side effects over the course of the clinical trial:
  - 61% were associated with hospitalization for drug relapse or similarly related treatment
  - 83% transpired during the follow-up period
  - One death in the buprenorphine condition was secondary to respiratory 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®

### Slide 93: BUP/NX Safety Profile was Excellent

Eighteen side effects were reported over course of clinical trial, including follow-up; 18 resulted in hospitalization and two resulted in death.

- Sixty-one percent were associated with hospitalization for drug relapse or similarly related treatment
- Eighty-three percent transpired during the follow-up period.
- The death that transpired was unexpected and discovered at the six month evaluation. It was associated with respiratory failure from a massive heart attack. The heart attack occurred four months following the completion of the taper and was not buprenorphine-naloxone related.
- Only one event – hematemesis (vomiting blood), presumably due to bleeding from an esophageal tear; it is possible the hematemesis was related to excessive hiccupping, which irritated the patient’s gastroesophageal mucosa and may have possibly been related to buprenorphine-naloxone.

### The Role of Psychosocial Treatment During Medically-Assisted Opioid Withdrawal



### Slide 94: The Role of Psychosocial Treatment During Medically-Assisted Opioid Withdrawal

This purpose of this study was to evaluate the efficacy of buprenorphine versus clonidine for conducting this 13-day taper. It was implemented in a variety of setting and participants received psychosocial treatment as provided by the treatment agency.

### 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

### Slide 95: The Role of Psychosocial Treatment

It was recognized by the investigators that participation in psychosocial counseling was very important. Previous research has also shown that participation in therapy helps to maximize the therapeutic effects of the medication.

All participants were provided with a workbook entitled ***Opioid Dependence: Handbook for Recovery Using Buprenorphine*** by Dr. Walter Ling. This ensured that participants received the same basic level of information. However, no instruction was given about how to use this book or about other psychosocial treatment. Agencies provided psychosocial care as usual in their environment.

The study's weakness is also its strength. We gave some guidance as to how to provide the psychosocial treatment. But the study was not set up to examine what type of psychosocial treatment was provided as data were not collected about this.

What the results indicate is that regardless of the type of psychosocial counseling provided, people receiving buprenorphine were more likely to be present and opioid free at the end of the taper than were those receiving clonidine.

This speaks well for the treatment across settings. However, additional research is needed to determine what type of treatment and/or what treatment elements are most effective in maximizing the results and helping the person to remain abstinent after the end of the taper.

### Key Lessons Learned from the CTN Experience

### Slide 96: Key Lessons Learned from the CTN Experience

In summary, let's look at the lessons that were learned from implanting this taper schedule in diverse inpatient and outpatient settings across the country.

<p style="text-align: center;"><b>Lessons Learned</b></p> <ol style="list-style-type: none"> <li>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.</li> <li>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.</li> </ol>	<p><b>Slide 97: Lessons Learned</b></p> <p>1) First, the medication was acceptable to the people taking it. 90% of the participants in the buprenorphine group successfully inducted onto the medication. That is, they received the first three doses and reached 16mg.</p> <p>2) Additionally, 3/4 of the participants completed the taper and were free from opioids on day 13. This indicates that this taper schedule is an effective way of engaging people in the treatment system.</p>
<p style="text-align: center;"><b>Lessons Learned (cont. in next)</b></p> <ol style="list-style-type: none"> <li>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.</li> <li>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.</li> </ol>	<p><b>Slide 98: Lessons Learned</b></p> <p>3) While the majority of participants experience some negative symptoms that required use of an ancillary medication, but generally this was for a symptom commonly seen from people withdrawing from opioids and not a negative effect of the medication.</p> <p>4) There were few serious adverse events in the trial and only one that <i>may</i> have been related to the medication. This indicates that buprenorphine is safe for use in these treatment settings.</p>
<p style="text-align: center;"><b>Lessons Learned (cont. in next)</b></p> <ol style="list-style-type: none"> <li>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.</li> <li>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.</li> </ol>	<p><b>Slide 99: Lessons Learned</b></p> <p>There is considerable information about buprenorphine among people seeking treatment for opioid dependence. Many of the programs had wait lists of people interested in entering the trial. Again this demonstrates and acceptance of the medication among the target group for treatment.</p> <p>More research is needed to answer questions such as:</p> <ul style="list-style-type: none"> <li>• Would patients do better with a shorter or longer taper schedule? (CTN research is going in presently to evaluate this)</li> <li>• What counseling is best coupled with this taper?</li> <li>• 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?</li> </ul>