



blending initiative
NIDA • SAMHSA

SHORT-TERM OPIOID WITHDRAWAL USING BUPRENORPHINE

Findings and Strategies
From a NIDA Clinical Trials
Network Study





Short Term Opioid Withdrawal Using Buprenorphine

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Short Term Opioid Withdrawal Using Buprenorphine

Findings and Strategies from a NIDA Clinical Trials Network Study

Background Information: NIDA/SAMHSA Blending Initiative

The National Institute on Drug Abuse (NIDA) and the Substance Abuse and Mental Health Services Administration (SAMHSA) have created a partnership to disseminate information to the addiction treatment field. Through the NIDA/SAMHSA Blending Initiative, special groups called Blending Teams meet to design dissemination strategies and develop research-based products. Members of these Blending Teams come from the NIDA-funded National Drug Abuse Treatment Clinical Trials Network (CTN) and the SAMHSA-funded Addiction Technology Transfer Center (ATTC) Network.

In the year 1999, NIDA created the National Drug Abuse Treatment 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. As the CTN research is completed, NIDA-funded researchers work with representatives from the ATTC network to provide the results and strategies for implementing these findings in clinical settings. This will decrease the time it takes for research to be incorporated into treatment settings and will thereby improve the quality of drug abuse treatment throughout the country.

Focus on Buprenorphine

In 2002, tablet formulations of buprenorphine were approved by the Food and Drug Administration (FDA) for the treatment of opiate addiction. Additionally, the CTN implemented and completed two clinical trials comparing the use of buprenorphine versus clonidine for short-term opioid withdrawal, 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 in how 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 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 comparing a 13-day detoxification with buprenorphine versus clonidine, in both inpatient and outpatient settings. The training will then provide instruction for implementing this protocol in treatment settings, including methods of evaluation and induction, the taper schedule, and use of ancillary medications during treatment.

How Are the PowerPoint Training Slides Organized?

The training package is designed to provide information and content for a 4-hour training. The training should be adapted by adding additional information to meet the needs of the audience. .

After providing a background of the Blending Initiative and the medications that will be discussed, this course, ***Short Term Opioid Withdrawal Using Buprenorphine***, will describe 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 method 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.

The training is designed as a stand-alone module. Alternatively, it can 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.

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 inducing the patients onto the medication.

As a rule of thumb, the training should be paced to allow approximately 2 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

- Computer with PowerPoint software installed (2003 or higher version) and LCD projector to project the PowerPoint training slides
- Flip chart paper and easel/white board, and pens to write down relevant information

Overall Training Notes

It is important to find as much out about the training participants 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-conducted with a physician or other medical personnel who has experience with buprenorphine treatment. If the trainer can pair with one of the physicians who was 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 be able 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.



Note to speaker



Activity



References

Buprenorphine Treatment: A Training for Multidisciplinary Addiction Professionals

Combining the Presentations

The NIDA/SAMHSA Blending Initiative has developed a suite of products on buprenorphine. The Buprenorphine Suite includes the following training curricula:

- Buprenorphine Treatment: A Training for Multidisciplinary Addiction Professionals
- Short Term Opioid Withdrawal Using Buprenorphine: Findings and Strategies From a NIDA Clinical Trials Network Study
- Buprenorphine Treatment for Young Adults: Findings and Strategies From a NIDA Clinical Trials Network Study

Each of these curricula is a self-contained training package that can be used to conduct a stand-alone training program. However, the Blending Team recognized that in many instances trainers may want to incorporate elements of two or all three curricula into a single training experience. Combining slides from the presentations may therefore be necessary. Below are instructions for combining slides for both PowerPoint 2007 and PowerPoint 1997-2003.

PowerPoint 2007

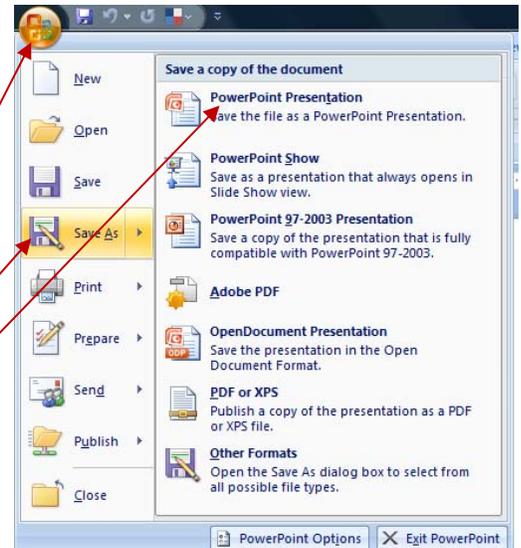
To combine slides into a single presentation, open all presentations from which you will be drawing slides. Determine which document will be the master document into which slides from the other presentation(s) will be copied. For instance, if you are conducting the *Buprenorphine Treatment: A Training for Multidisciplinary Addiction Professionals*, this would be your master document. It is recommended that you save a new copy of this presentation before altering it in order to preserve the original training content.

I. Save a new copy of your presentation.



(1) Click on the program icon in the upper right corner of your screen and then (2) click on **Save As** from the drop down menu. Next, (3) click on **PowerPoint Presentation**. A dialogue box will appear that will allow you to give the presentation a name and location.

Click in this order:
1. Program Icon
2. Save As
3. PowerPoint Presentation



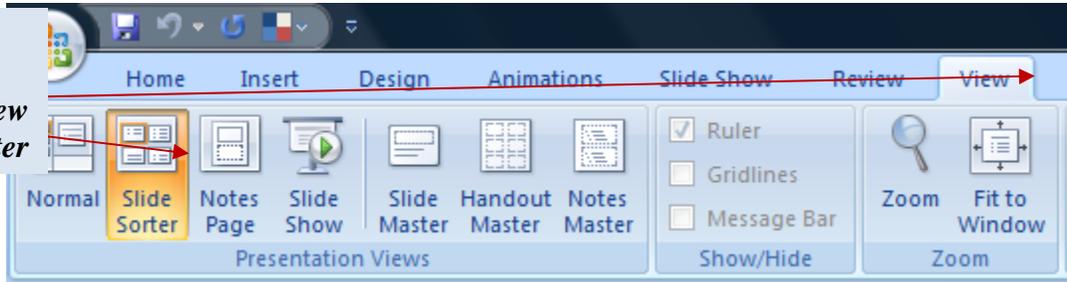
II. Open the presentation from which slides will be copied.

III. Select Slide Sorter view.

Go to the Slide Sorter view by (1) clicking on **View** from the menu at the top of the page and then (2) clicking **Slide Sorter** located on the left side of the page near the top.

Click in this order:

1. View
2. Slide Sorter



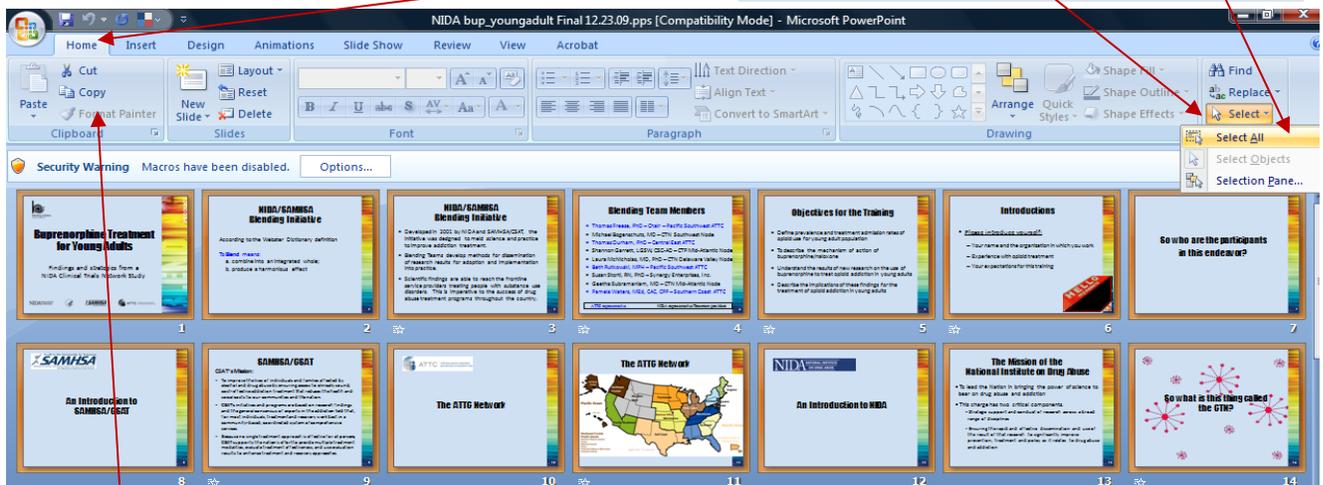
IV. Select the slides to be copied.

Slides can be copied in two ways. You can select all slides in the presentation, or you can choose only certain slides to copy. Instructions for each are presented below

Select all slides in presentation. Copy all slides in the presentation by (1) clicking on **Home** from the menu at the top of the page and then (2) clicking on **Select** on the far right side of the page near the top. Next, (3) click on **Select All** from the drop down menu. All slides in the presentation will be highlighted in yellow.

Click in this order:

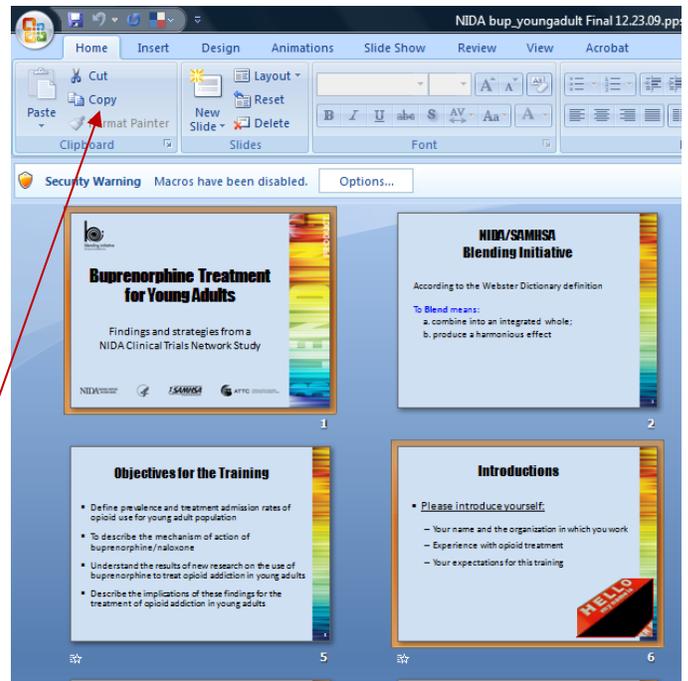
1. Home
2. Select
3. Select All



Finally, (4) **copy the selected slides to the clipboard** by clicking on **Copy** on the upper left of the screen.

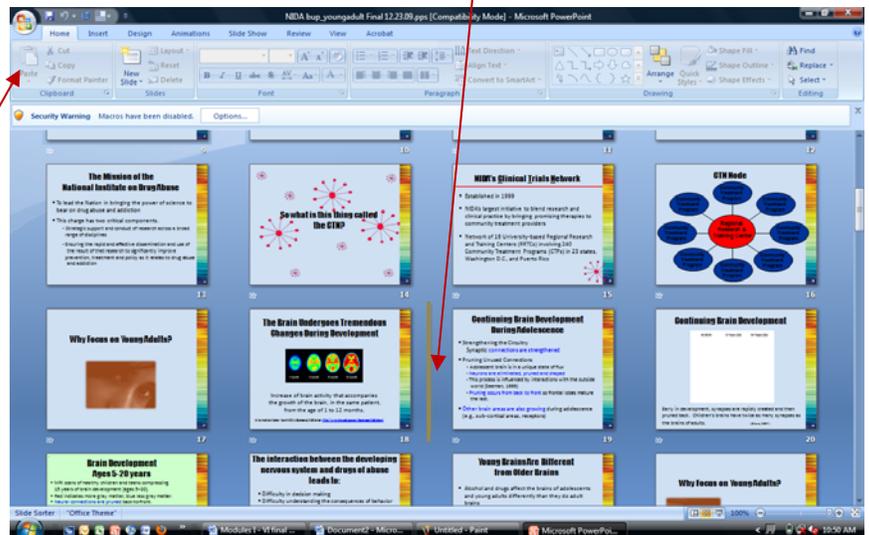
Select specific slides to copy. To copy only certain slides (rather than all of them), on your computer keyboard, hold down the control (**Ctrl**) button. While holding down **Ctrl**, click on the slides that you want to copy into the combined presentation. Only slides on which you click will be selected (highlighted in yellow). In the close-up example on the right, Slides 1 and 6 are selected (have a yellow box around them). Slides 2 and 5 are not selected. Once you have clicked on all the slides that you want to select, let go of the **Ctrl** key and then click on **Copy** on the upper left side of the page.

Note: You may want to practice copying a few slides at a time until you are comfortable with this procedure.



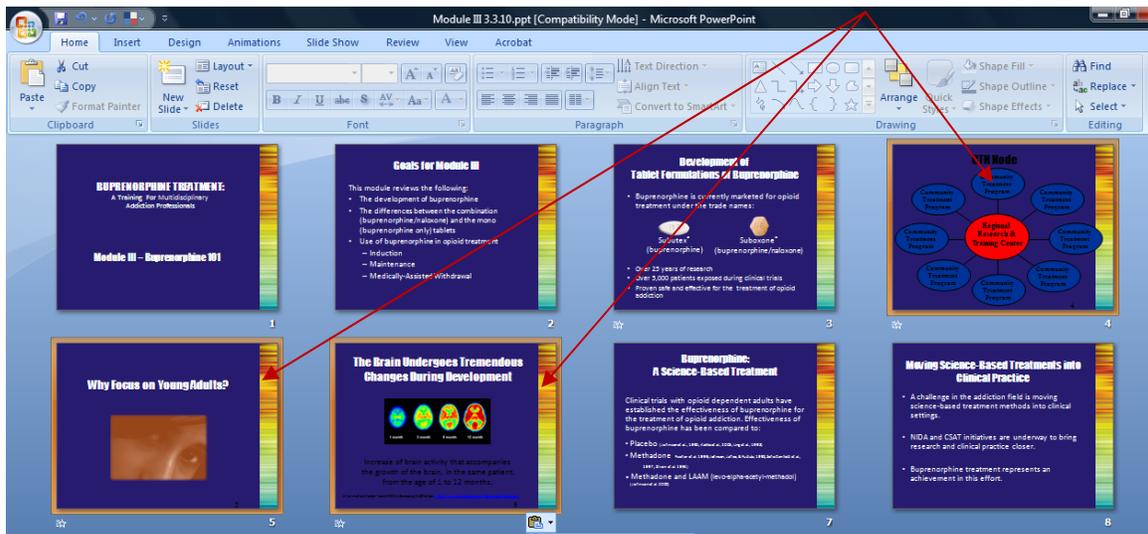
V. Paste the copied slides into your presentation.

Open your master presentation (the presentation into which the slides are to be copied). Again go to the **Slide Sorter** view as described in Step III above. (1) Click in the space between the slides where you would like the copied slides to appear. A flashing line will appear between the slides. In this example, the copied slides will appear after Slide 18. Then (2) click on **Paste** in the upper left corner.



VI. Maintain original formatting.

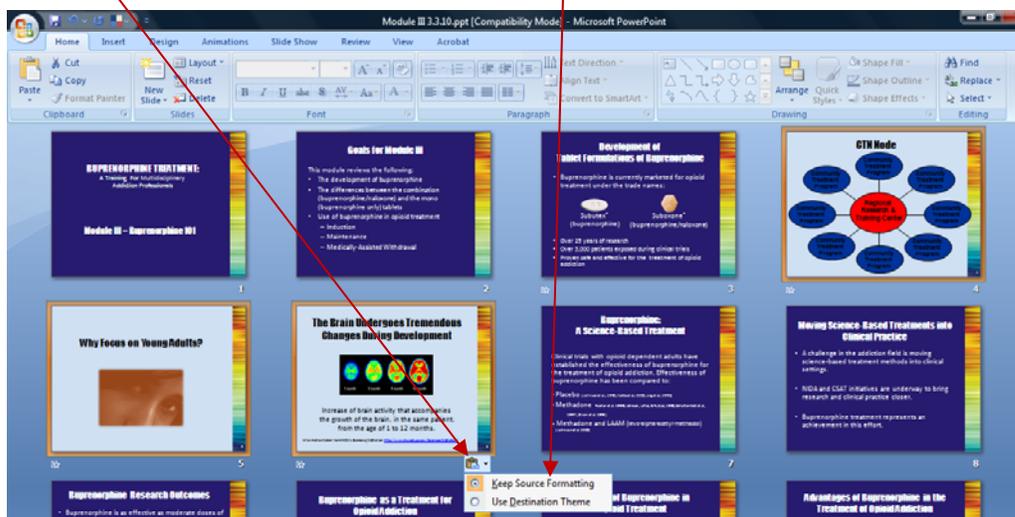
When copying slides from one presentation to the other, the formatting of the copied slides will be altered to match the presentation into which they are inserted. However, this often leads to significant formatting irregularities. In the example below, Slides 4 to 6 were inserted using the method described above. Notice that some of the text is too dark and difficult to read with the new formatting.



To prevent this problem, it is recommended that the inserted slides maintain the formatting of the original presentation. The following steps show how to do this.

After pasting the slides into the presentation, you will notice that a small clipboard appears near the last inserted slides.

- (1) Click on the clipboard and then (2) click on **Keep Source Formatting** in the drop-down menu that appears.



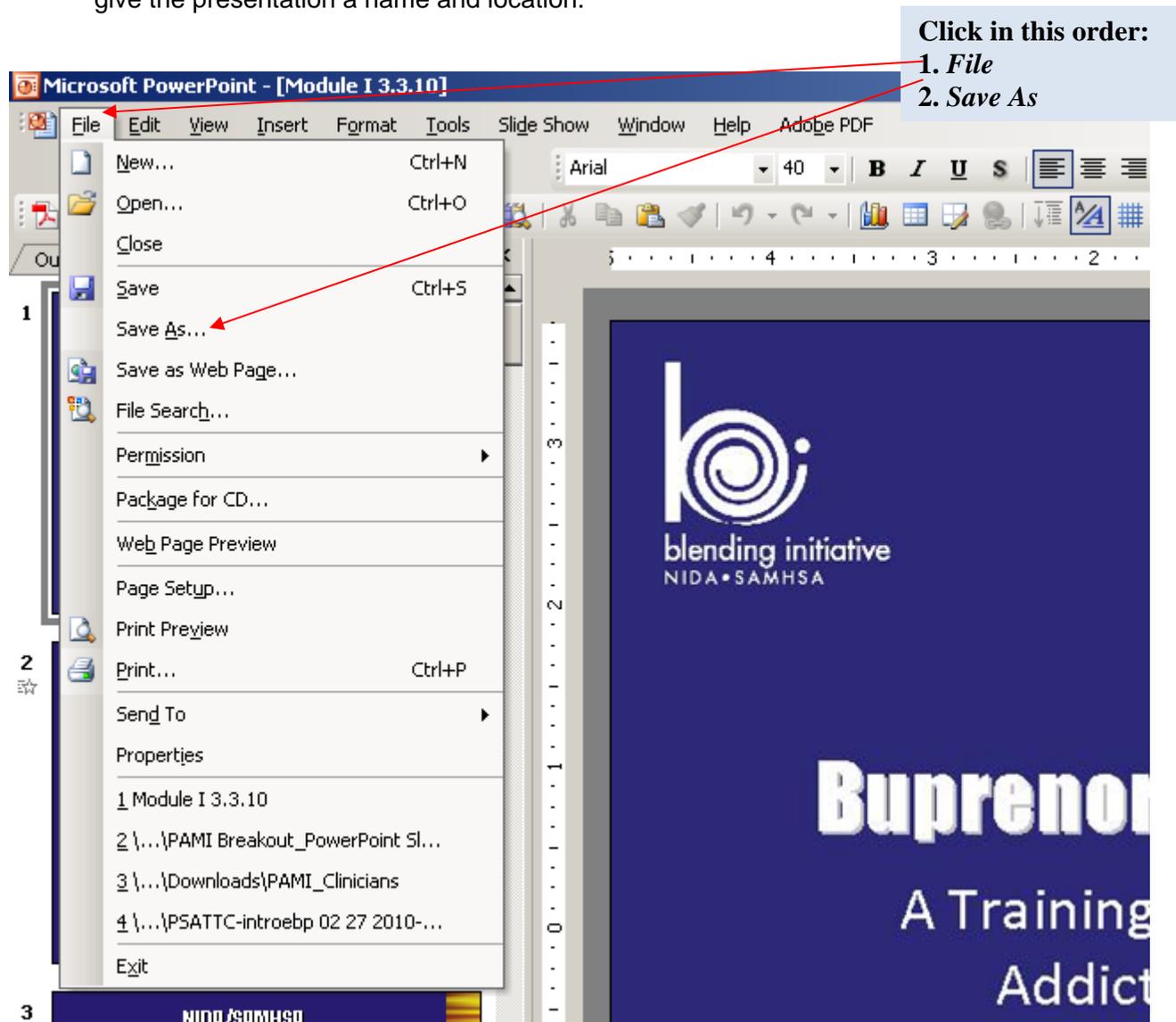
This will restore the formatting from the original presentation and ensure that the slides are legible when projected during a training session.

PowerPoint 1997-2003

To combine slides into a single presentation, open all presentations from which you will be drawing slides. Determine which document will be the master document into which slides from the other presentations will be copied. For instance, if you are conducting the *Buprenorphine Treatment: A Training for Multidisciplinary Addiction Professionals*, this would be your master document. It is recommended that you save a new copy of this presentation before altering it in order to preserve the original training content.

I. Save a new copy of your presentation.

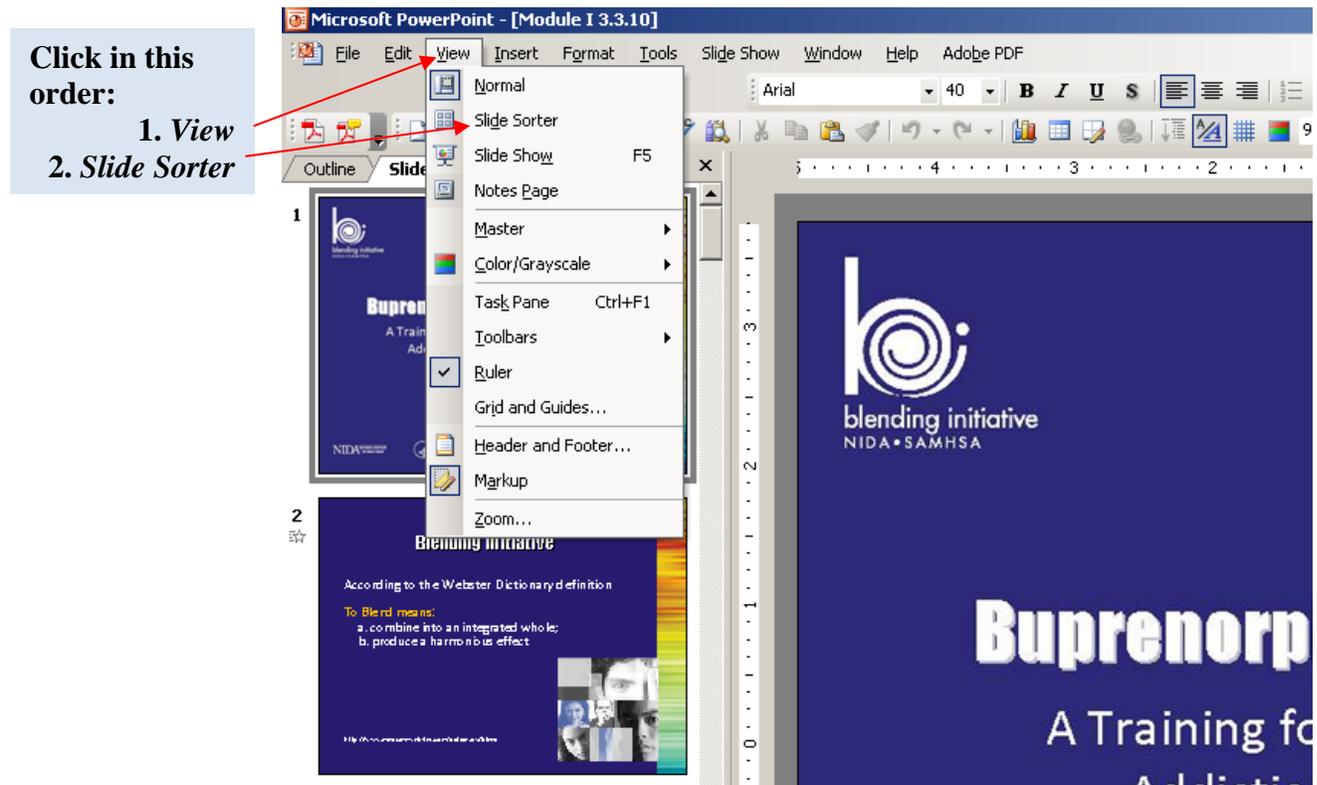
(1) Click on the **File** button in the upper left corner of the toolbar and then (2) click on **Save As** from the drop-down menu. A dialogue box will appear that will allow you to give the presentation a name and location.



II. Open the presentation from which slides will be copied.

III. Select Slide Sorter view.

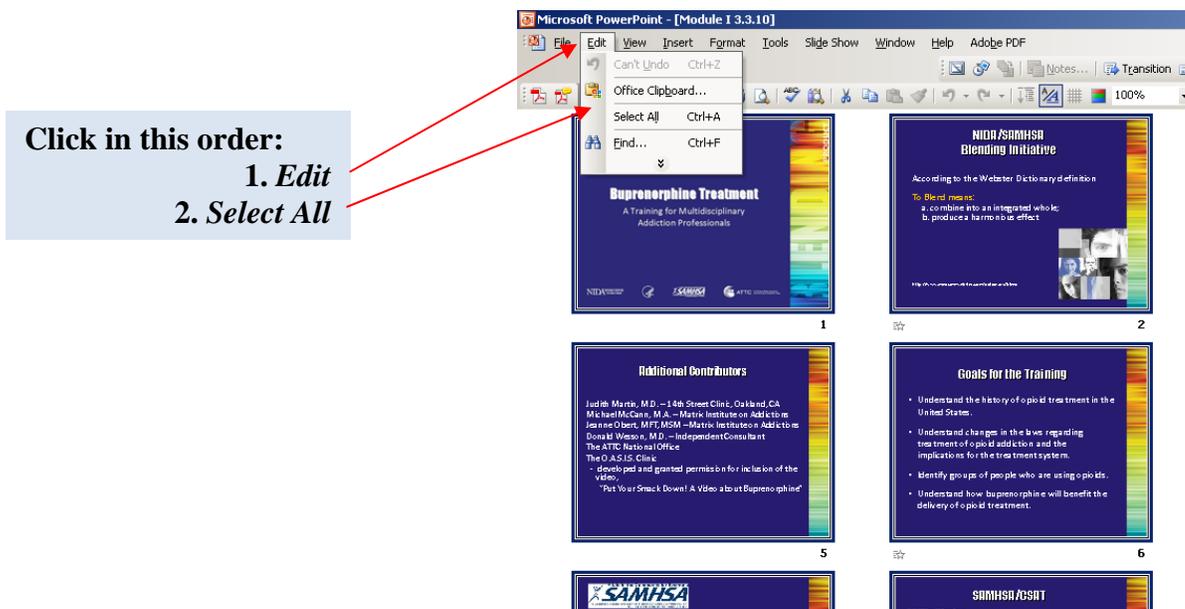
Go to the Slide Sorter view by (1) clicking on **View** from the menu at the top of the page and then (2) clicking **Slide Sorter** from the drop-down menu.



IV. Select the slides to be copied.

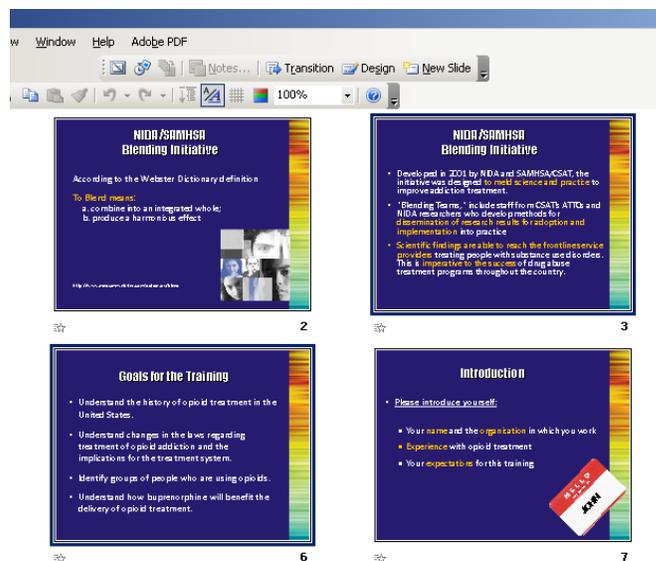
Slides can be copied in two ways. You can select all slides in the presentation, or you can choose only certain slides to copy. Instructions for each are presented below.

Select all slides in presentation. Copy all slides in the presentation by (1) clicking on **Edit** in the top toolbar and then (2) clicking **Select All** from the drop-down menu. All slides in the presentation will be highlighted in dark blue.



Finally, (3) click on the **Edit** button in the top toolbar and then click on **Copy** from the drop-down list.

Select specific slides for copying. To copy only certain slides (rather than all of them), on your computer keyboard, hold down the control (**Ctrl**) button. While holding down **Ctrl**, click on the slides that you want to copy into the combined presentation. Only slides on which you click will be selected (highlighted in dark blue). In the close-up example on the right, Slides 3 and 6 are selected (have a dark blue border around them). Once you have clicked on all the slides that you want to select, let go of the **Ctrl** key and then click on the **Edit** button in the top toolbar and then click on **Copy** from the drop-down menu.



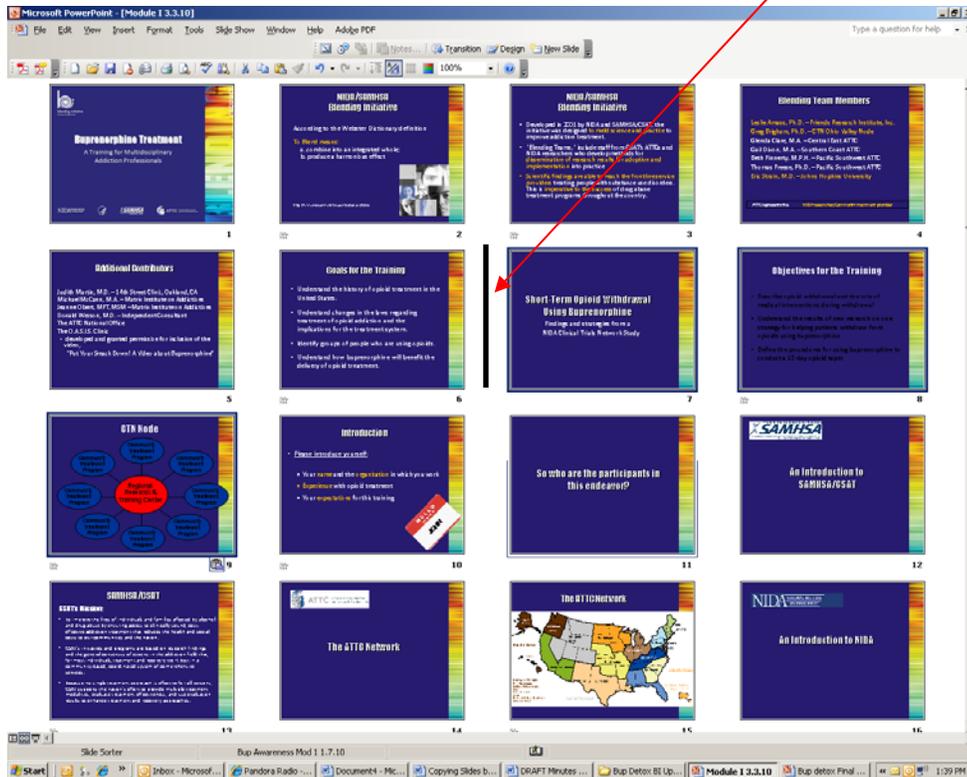
Note: You may want to practice copying a few slides at a time until you are comfortable with this procedure.

V. Paste the copied slides into your presentation.

Open your master presentation (the presentation into which the slides are to be copied). Again go to the **Slide Sorter View** as described in Step III above. (1) Click in the space between the slides where you would like the copied slides to appear. A flashing line will appear between the

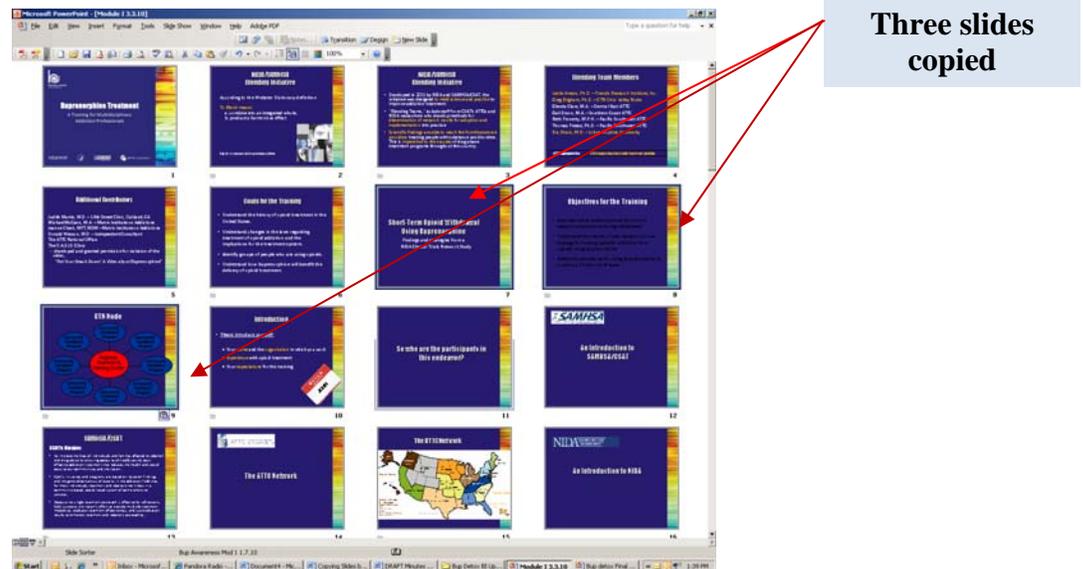
slides. In this example, the copied slides will appear after Slide 6. Then (2) click on **Edit** and then **Paste** in the upper left corner.

Click in space where slides are to be inserted.



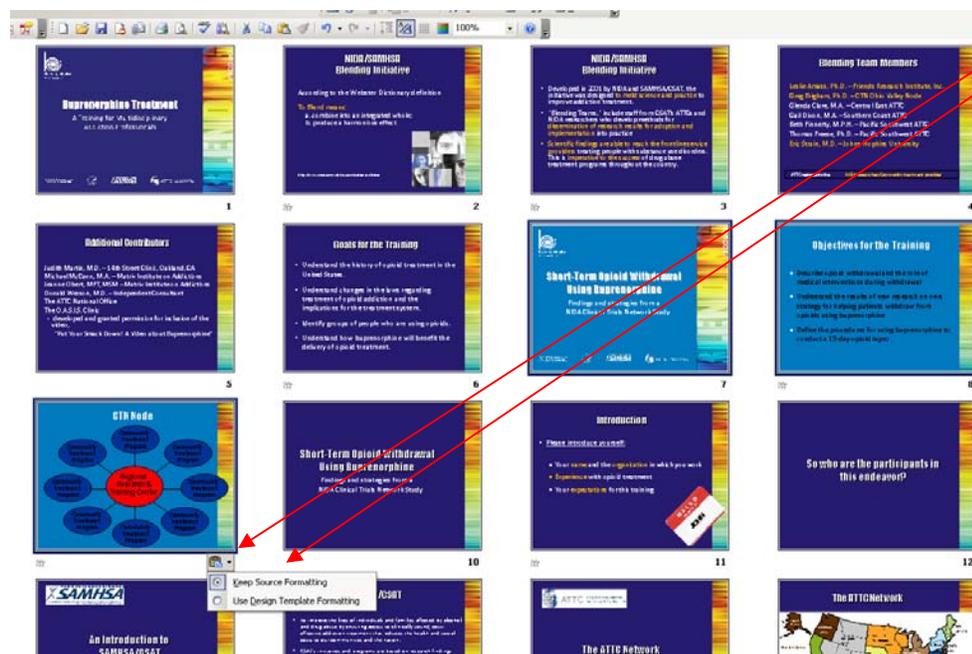
VI. Maintain original formatting.

When copying slides from one presentation to the other, the formatting of the copied slides will be altered to match the presentation into which they are inserted. However, this often leads to significant formatting irregularities. In the example below, Slides 7 to 9 were inserted into this presentation using the method described above. Notice that some of the text is too dark and difficult to read with the new formatting.



To prevent this problem, it is recommended that the inserted slides maintain the formatting of the original presentation. The following steps will show you how to do this.

After pasting the slides into the presentation, you will notice that a small clipboard appears near the last inserted slide.



(1) Click on the clipboard and then (2) click on **Keep Source Formatting** in the drop-down menu that appears.

This will restore the formatting from the original presentation and ensure that the slides are legible when projected during a training session.

Short Term Opioid Withdrawal Using Buprenorphine

Slide-By-Slide Trainer Notes

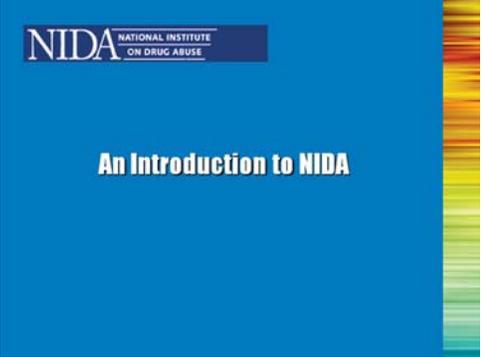
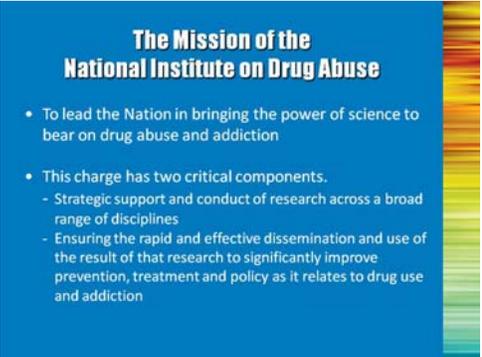
The notes below contain information that can be presented with each slide. This information is designed as a guidepost and can be adapted to meet the needs of the local training situation. Information can be added or deleted at the discretion of the trainer(s).

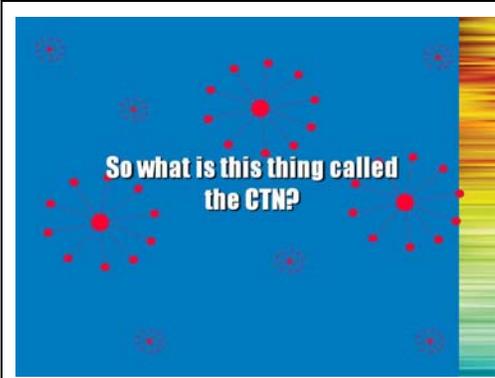
 <p>Slide 1: Short Term Opioid Withdrawal Using Buprenorphine Findings and strategies from a NIDA Clinical Trials Network Study</p> <p>NIDA SAMHSA ATTC</p>	<p>Slide 1: Short Term Opioid Withdrawal Using Buprenorphine</p> <p><i>Welcome participants and take care of housekeeping details such as location of restrooms, turning off cell phones, participate actively, etc.</i></p> <p><i>Briefly describe the development of the Blending Team product, as well as the purpose of the training as described 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><i>Reiterate that throughout the training, the term “patient” has been used to refer to the individual seeking treatment. This terminology reflects the medicalized nature of buprenorphine treatment and underscores the fact that the treatment is largely physician-driven. The use of this term may be inconsistent with the vocabulary in common usage in the addiction treatment setting.</i></p> <p><i>Also reiterate that throughout the training, the term “medication” has been used to refer to buprenorphine and buprenorphine/naloxone. This terminology again reflects the medicalized nature of buprenorphine treatment and underscores the difference between a drug of abuse and medication used for the treatment of opioid treatment and medically-assisted withdrawal.</i></p>	<p>Slide 1</p> 
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<p>NIDA/SAMHSA Blending Initiative</p> <p>According to the Webster Dictionary definition</p> <p>To Blend means:</p> <ol style="list-style-type: none"> combine into an integrated whole; produce a harmonious effect  <p><small>http://www.merriam-webster.com/dictionary/blend</small></p>	<p>Slide 2: NIDA/SAMHSA Blending Initiative</p> <p><i>Share the definition of “blend” based upon the Webster dictionary.</i></p> <p>Reference:</p> <p>blend. (2010). In <i>Merriam-Webster Online Dictionary</i>. Retrieved March 16, 2010, from http://www.merriam-webster.com/dictionary/blend</p>	<p>Slide 2</p>  
<p>NIDA/SAMHSA Blending Initiative</p> <ul style="list-style-type: none"> Developed in 2001 by NIDA and SAMHSA/CSAT, the initiative was designed to meld science and practice to improve addiction treatment. “Blending Teams,” include staff from CSAT’s ATTCs and NIDA researchers who develop methods for dissemination of research results for adoption and implementation into practice. Scientific findings are able to reach the frontline service providers treating people with substance use disorders. This is imperative to the success of drug abuse treatment programs throughout the country. 	<p>Slide 3: NIDA/SAMHSA Blending Initiative</p> <p>Developed in 2001 by the National Institute on Drug Abuse (NIDA) and the Substance Abuse and Mental Health Services Administration’s (SAMHSA) Center for Substance Abuse Treatment (CSAT), the NIDA/SAMHSA Blending Initiative is designed to meld science and practice together to improve substance use disorder treatment. The primary goal of this initiative is to develop methods for disseminating research findings that will accelerate the adoption and implementation of research-based drug abuse treatment into community-based practice.</p> <p>Blending Products are designed to shorten the time that it takes scientific findings to become available in a usable way for frontline service providers. This is imperative for successful outcomes of clients in addiction treatment programs throughout the country.</p>	<p>Slide 3</p>
<p>Blending Team Members</p> <p>Thomas Freese, Ph.D. – Chair – Pacific Southwest ATTC 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</p> <p>ATTC representative NIDA researcher/Community treatment provider</p>	<p>Slide 4: Blending Team Members</p> <p>Blending Teams are composed of NIDA-funded researchers, community-based substance abuse treatment practitioners and trainers from SAMHSA’s Addiction Technology Transfer Center (ATTC) Network who work closely together to develop the NIDA/SAMHSA Blending products.</p> <p>Note to the Trainer(s): Acknowledge the members of the Blending Team who created this module. Note that the membership consisted of four ATTC representatives and three NIDA-funded researchers and community treatment providers.</p>	<p>Slide 4</p> 

<p>Objectives for the Training</p> <ul style="list-style-type: none"> • Describe opioid withdrawal and the role of medical interventions during withdrawal • Understand the results of new research on one strategy for helping patients withdraw from opioids using buprenorphine • Define the procedures for using buprenorphine to conduct a 13-day opioid taper 	<p>Slide 5: Objectives for the Training</p> <p>There are three primary objectives for this training:</p> <ul style="list-style-type: none"> • To describe opioid withdrawal and the role of medical interventions during withdrawal • To understand the results of new research on one strategy for helping patients withdraw from opioids using buprenorphine • To define procedures for using buprenorphine to conduct a 13-day opioid taper 	<p>Slide 5</p>
<p>Introductions</p> <p>Please introduce yourself:</p> <ul style="list-style-type: none"> - Your name and the organization in which you work - Experience with opioid treatment - Your expectations for this training 	<p>Slide 6: Introductions</p> <p><i>For smaller groups (20 or less): 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><i>For larger groups: Personal introductions will take too much time to complete. Omit this slide and proceed by asking people to identify their role in the treatment system by raising their hand.</i></p> <p>At minimum, ask: Who is:</p> <ul style="list-style-type: none"> • A direct treatment provider • A counselor • A nurse • A physician • A social worker • An administrator • An educator • Anyone that I missed? 	<p>Slide 6</p> 
<p>So who are the participants in this endeavor?</p>	<p>Slide 7: So who are the participants in this endeavor?</p> <p>So now we will introduce the key participants who helped put these materials together.</p>	<p>Slide 7</p>

 <p>An Introduction to SAMHSA/CSAT</p>	<p>Slide 8: An Introduction to SAMHSA/CSAT</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>	<p>Slide 8</p>
<p>SAMHSA/CSAT</p> <p>CSAT's Mission:</p> <ul style="list-style-type: none"> • To improve the lives of individuals and families affected by alcohol and drug abuse by ensuring access to clinically sound, cost-effective addiction treatment that reduces the health and social costs to our communities and the nation. • CSAT's initiatives and programs are based on research findings and the general consensus of experts in the addiction field that, for most individuals, treatment and recovery work best in a community-based, coordinated system of comprehensive services. • Because no single treatment approach is effective for all persons, CSAT supports the nation's effort to provide multiple treatment modalities, evaluate treatment effectiveness, and use evaluation results to enhance treatment and recovery approaches. 	<p>Slide 9: SAMHSA/CSAT</p> <p>Read CSAT mission.</p> <p>Note to the Trainer(s): <i>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.</i></p>	<p>Slide 9</p> 
 <p>The ATTC Network</p>	<p>Slide 10: The ATTC Network</p> <p>One of the major vehicles that SAMHSA has for ensuring that the workforce is adequately trained is the Addiction Technology Transfer Center (ATTC) Network.</p>	<p>Slide 10</p>

	<p>Slide 11: The ATTC Network</p> <p>Fourteen regional Centers and a National Office constitute the ATTC Network, which is dedicated to identifying and advancing opportunities for improving addiction treatment.</p> <p>The vision of the ATTC Network is to unify science, education and services to transform the lives of individuals and families affected by alcohol and other drug addiction.</p> <p>Serving the 50 United 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.</p>	<p>Slide 11</p>
	<p>Slide 12: An Introduction to the National Institute on Drug Abuse</p> <p>The National Institute on Drug Abuse (NIDA) was established in 1974. In October 1992, it became part of the National Institutes of Health, Department of Health and Human Services.</p> <p>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 NIDA.</p>	<p>Slide 12</p>
 <p>The Mission of the National Institute on Drug Abuse</p> <ul style="list-style-type: none"> • To lead the Nation in bringing the power of science to bear on drug abuse and addiction • This charge has two critical components. <ul style="list-style-type: none"> - Strategic support and conduct of research across a broad range of disciplines - Ensuring the rapid and effective dissemination and use of the result of that research to significantly improve prevention, treatment and policy as it relates to drug use and addiction 	<p>Slide 13: The Mission of NIDA</p> <p>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 <i>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.</i> The scientific knowledge that is generated through NIDA-funded research is a critical element to improving the overall health of the Nation. The goal of NIDA is to ensure that science, not ideology or anecdote, forms the foundation for all of our Nation's drug abuse reduction efforts.</p>	<p>Slide 13</p>



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. This presents a problem when trying to apply these findings about new treatments into community-based treatment programs, which typically serve diverse populations. To address this problem, NIDA established the National Drug Abuse Treatment Clinical Trials Network (CTN).

Slide 14



Slide 15: NIDA's Clinical Trials Network

The mission of the CTN is twofold:

- Conduct studies of behavioral, pharmacological, and integrated behavioral and pharmacological interventions to determine 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.

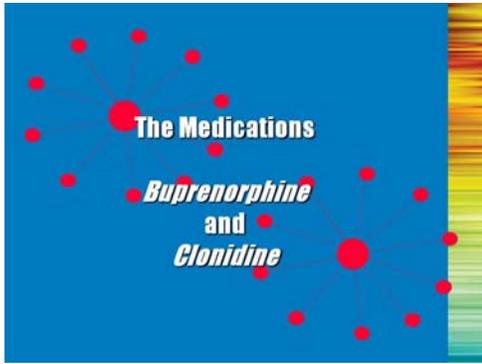
Slide 15



Slide 16: CTN Node

The CTN is comprised of Nodes that are dispersed across the country. Each Node has one Regional Research Training Center (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.

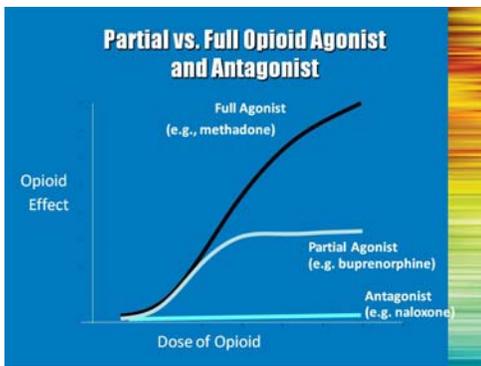
Slide 16



Slide 17: The Medications: Buprenorphine and Clonidine (Transition Slide)

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. In the next section we will look at the mechanism of action of these medications and issues pertaining to their efficacy and safety.

Slide 17



Slide 18: Partial vs. Full Opioid Agonist and Antagonist

This slide graphically depicts the different types of opioids (whether they are prescribed medications, such as Vicodin or methadone, or an illicit substance, like heroin).

Move forward to reveal first line (full agonist)

Full agonists (e.g., heroin, opium, Vicodin, methadone, etc.) fully activate the receptors so that the more you use, the more effect you experience. If someone continues to use, they will eventually experience overdose and, possibly, death.

The following metaphor may be helpful in explaining the differences between the types of opioids:

Opioid agonists work like having the right key to a door. You put the key in the lock, the lock turns and the door opens completely.

Move forward to reveal the next line (antagonists)

Opioid antagonists (e.g., naltrexone, naloxone) fill the receptors and block the action of other opioids. If the person has used an opioid agonist, the antagonist will replace it on the receptor and the person will experience withdrawal. If the person is stable on an antagonist, and uses another opioid, the antagonist will block the effects, preventing the user from experiencing the high.

The door metaphor continued:

Opioid antagonists work like having the wrong key to a door. You put the key in the lock; the door remains locked and will not open. Additionally, since the key is in the lock, no other key can be put in the lock (even if it is the right key for that door) until the wrong key is removed.

Move forward to reveal the last line (partial agonists)

Opioid partial agonists (e.g., buprenorphine) are in the middle. At lower doses, they work just like agonists, filling the receptor and preventing withdrawal symptoms. However, as the dose increases, a ceiling effect occurs so that if more is used, no more effect is achieved. This ceiling effect applies both to opioid euphoria (they don't feel high), and to the respiratory suppression (making overdose less likely).

The door metaphor continued:

Opioid partial agonists work like having the right key to a door, but the chain is on the door. The key goes in and opens the door, but it will only open so far.

Slide 18



Buprenorphine

- Partial Opioid Agonist
 - > Has effects of **typical opioid agonists** at **lower doses**
 - > Produces a **ceiling effect** at **higher doses**
 - > Binds strongly to opioid receptor and is **long-acting**
- **Safe and effective** therapy for opioid maintenance and detoxification in adults
- Slow to dissociate from receptors so effects last even if one daily dose is missed (reduced effects may be felt few days after prolonged use).
- **FDA approved** for use with opioid dependent persons age **16 and older**

Slide 19: Buprenorphine

As mentioned in the previous slide, buprenorphine is a partial agonist. It has been shown to be safe and effective for the treatment of opioid dependence both as a maintenance agent and for use during withdrawal from opioids.

Buprenorphine binds to the receptors very strongly (affinity) and comes off very slowly (dissociation). This makes it a very long-lasting medication that continues to be effective even if a dose is missed.

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

Another advantage is that the FDA approval for the medication is for opioid dependent individuals age 16 and older. *It is possible to use the medication with younger adolescents if determined medically appropriate (benefits outweigh the risks). However, this would be off-label use and the patients must be monitored very closely due to the lack of clinical research data.*

It may be worth noting that buprenorphine is the only medication with FDA approval that is not schedule II (whereas, methadone is schedule II), and that only Suboxone and Subutex are approved.

*Although Buprenex® (injectable formulation of buprenorphine) and Talwin® (Pentazocine) are also partial opioid agonists and approved for the treatment of pain; they **ARE NOT** approved for the treatment of opioid addiction.*

Note to the Trainer(s): *It is important to review the definition of “affinity”, “intrinsic activity,” and “dissociation” (CSAT, 2004) as these terms will be referenced throughout the module.*

- *Affinity: The strength with which a drug binds to its receptor*
- *Intrinsic activity: the degree to which a drug activates its receptors*
- *Dissociation: a measure of the disengagement or uncoupling of the drug from the receptor.*

Reference:

Center for Substance Abuse Treatment. *Clinical Guidelines for the Use of Buprenorphine in the Treatment of Opioid Addiction*. Treatment Improvement Protocol (TIP) Series 40. DHHS Publication No. (SMA) 04-3939. Rockville, MD: Substance Abuse and Mental Health Services Administration, 2004.

Slide 19



Development of Tablet Formulations of Buprenorphine

- Buprenorphine is currently marketed for opioid treatment under the trade names:



Subutex®
(buprenorphine)



Suboxone®
(buprenorphine/naloxone)

- Over 25 years of research
- Over 5,000 patients exposed during clinical trials
- Proven safe and effective for the treatment of opioid addiction

Slide 20: Development of Tablet Formulations of Buprenorphine

Buprenorphine was developed by a pharmaceutical company called Reckitt Benckiser. They had exclusive marketing rights until Fall 2009, and distribute the medication as:

Subutex® = a sublingual tablet containing buprenorphine hydrochloride only

Suboxone® = a sublingual tablet containing both buprenorphine hydrochloride and naloxone hydrochloride in a 4:1 ratio

Reckitt Benckiser's exclusive rights expired in the fall of 2009, so generic versions of the medication may become available in the future.

Buprenorphine/naloxone is the focus of U.S. marketing efforts, even though both formulations are available in the United States.

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.

Slide 20

Buprenorphine: A Science-Based Treatment

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

- **Placebo** (Johnson et al., 1995; Kakko et al., 2003; Ling et al., 1998)
- **Methadone** (Fischer et al., 1999; Johnson, Jaffe, & Fudala, 1992; Schottenfeld et al., 1997; Strain et al., 1994)
- **Methadone and LAAM (levo-alpha-acetyl-methadol)** (Johnson et al., 2000)

Slide 21: Buprenorphine: A Science-Based Treatment

Slide 21

In the development of the medication, the effectiveness of buprenorphine has been compared to that of other currently available medications. These studies have shown that buprenorphine treatment:

- is more effective than placebo; and
- has similar effectiveness to moderate doses of methadone and LAAM.

References:

Fischer, G., Gombas, W., Eder, H., Jagsch, R., Peterzell, A., Stuhlinger, G., et al. (1999). Buprenorphine versus methadone maintenance for the treatment of opioid dependence. *Addiction, 94*(9), 1337-1347.

Johnson, R. E., Jaffe, J. H., & Fudala, P. J. (1992). A controlled trial of buprenorphine treatment for opioid dependence. *Journal of the American Medical Association, 267*, 2750–2755.

Johnson, R. E., Eissenberg, T., Stitzer, M. L., Strain, E. C., Liebson, I. A., & Bigelow, G. E. (1995) A placebo controlled clinical trial of buprenorphine as a treatment for opioid dependence. *Drug and Alcohol Dependence, 40*(1), 17-25.

Johnson, R. E., Chutuape, M. A., Strain, E. C., Walsh, S. L., Stitzer, M. L., & Bigelow, G. E. (2000). A comparison of levomethadyl acetate, buprenorphine, and methadone for opioid dependence. *New England Journal of Medicine, 343*(18), 1290-1297.

Kakko, J., Svanborg, K., Kreek, M., & Heilig, M. (2003). 1-year retention and social function after buprenorphine-assisted relapse prevention treatment for heroin dependence in Sweden: A randomised, placebo-controlled trial. *The Lancet, 361*(9358), 662-668.

Ling, W., Charuvastra, C., Collins, J. F., Batki, S., Brown, L. S., Jr., Kintaudi, P., et al. (1998) Buprenorphine maintenance treatment of opiate dependence: A multicenter, randomized clinical trial. *Addiction, 93*, 475–486.

Schottenfeld, R. S., Pakes, J. R., Oliveto, A., Ziedonis, D., & Kosten T. R. (1997). Buprenorphine vs methadone maintenance treatment for concurrent opioid dependence and cocaine abuse. *Archives of General Psychiatry, 54*, 713–720.

Strain, E. C., Stitzer, M. L., Liebson, I. A., & Bigelow, G. E. (1994). Comparison of buprenorphine and methadone in the treatment of opioid dependence. *American Journal of Psychiatry, 151*, 1025–1030.



Buprenorphine Research Outcomes

- Buprenorphine is as effective as moderate doses of methadone (Fischer et al., 1999; Johnson, Jaffe, Fudala, 1992; Ling et al., 1996; Schottenfeld et al., 1997; Strain et al., 1994).
- Buprenorphine is as effective as moderate doses of LAAM (Johnson et al., 2000).
- Buprenorphine's partial agonist effects make it mildly reinforcing, encouraging medication compliance (Ling et al., 1998).
- After a year of buprenorphine plus counseling, 75% of patients retained in treatment compared to 0% in a placebo-plus-counseling condition (Kakko et al., 2003).

Slide 22: Buprenorphine Research Outcomes

Clinical trials have established the effectiveness of buprenorphine for the treatment of opioid addiction. The clinical studies have shown the following about buprenorphine:

Bullet #1: Patients on buprenorphine did as well as patients on a moderate dose of methadone (e.g., 60 mg).

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).

Bullet #3: Patients found that taking buprenorphine was a pleasant experience, which encouraged them to be compliant.

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.

References: (Bullet #1)

Fischer, G., Gombas, W., Eder, H., Jagsch, R., Peternell, A., Stuhlinger, G., et al. (1999). Buprenorphine versus methadone maintenance for the treatment of opioid dependence. *Addiction*, 94(9), 1337-1347.

Johnson, R. E., Jaffe, J. H., & Fudala, P. J. (1992). A controlled trial of buprenorphine treatment for opioid dependence. *Journal of the American Medical Association*, 267, 2750-2755.

Schottenfeld, R. S., Pakes, J. R., Oliveto, A., Ziedonis, D., & Kosten T. R. (1997). Buprenorphine vs methadone maintenance treatment for concurrent opioid dependence and cocaine abuse. *Archives of General Psychiatry*, 54, 713-720.

Strain, E. C., Stitzer, M. L., Liebson, I. A., & Bigelow, G. E. (1994). Comparison of buprenorphine and methadone in the treatment of opioid dependence. *American Journal of Psychiatry*, 151, 1025-1030.

Reference: (Bullet #2)

Johnson, R. E., Chutuape, M. A., Strain, E. C., Walsh, S. L., Stitzer, M. L., & Bigelow, G. E. (2000). A comparison of levomethadyl acetate, buprenorphine, and methadone for opioid dependence. *New England Journal of Medicine*, 343(18), 1290-1297.

Reference: (Bullet #3)

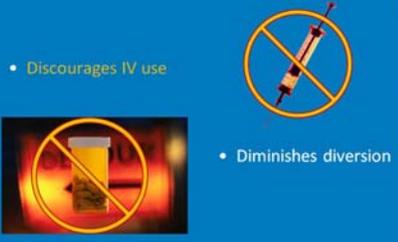
Ling, W., Charuvastra, C., Collins, J. F., Batki, S., Brown, L. S., Jr., Kintaudi, P., et al. (1998) Buprenorphine maintenance treatment of opiate dependence: A multicenter, randomized clinical trial. *Addiction*, 93, 475-486.

Reference: (Bullet #4)

Kakko, J., Svanborg, K., Kreek, M., & Heilig, M. (2003). 1-year retention and social function after buprenorphine-assisted relapse prevention treatment for heroin dependence in Sweden: A randomized, placebo-controlled trial. *The Lancet*, 361(9358), 662-668.

Slide 22



<p>Why did they make two formulations?</p> 	<p>Slide 23: Why did they make two formulations?</p> <p>As previously stated, the focus of marketing in the United States and the formulation used in the CTN studies is the buprenorphine/naloxone combination. Understanding why this combination was made is critical.</p>	<p>Slide 23</p>
<p>Advantages of Buprenorphine/Naloxone</p> <ul style="list-style-type: none"> Discourages IV use Diminishes diversion 	<p>Slide 24: Advantages of Buprenorphine/Naloxone</p> <p>The buprenorphine/naloxone formulation has some advantages compared with the buprenorphine only formulation:</p> <ul style="list-style-type: none"> It discourages injection of the product because, when injected, the naloxone will lead to withdrawal, whereas when taken sublingually as prescribed, it will not have that effect. Because of the above point, the combination tablet lowers the likelihood that the medication will be diverted. 	<p>Slide 24</p>
<p>Use of Buprenorphine: Studies on Cost-Effectiveness</p> <ul style="list-style-type: none"> Medication costs are only one factor. Costs of providing treatment also include costs associated with clinic visits, staff time, etc. These costs are greater for methadone. While not yet studied in young adults, research on adult populations has demonstrated cost effectiveness of buprenorphine across several indicators. 	<p>Slide 25: Use of Buprenorphine: Studies on Cost-Effectiveness</p> <p>There has been much discussion regarding the costs associated with the use of buprenorphine for the treatment of opioid dependence. When considering the costs of providing treatment, you must also include costs associated with clinic visits, staff time, and general operating and facility expenditures.</p> <p>Recently, research conducted on adult populations has demonstrated the utilization of buprenorphine is cost effective across several indicators.</p>	<p>Slide 25</p>

Use of Buprenorphine: Studies on Cost-Effectiveness

- A cost effective comparison of buprenorphine versus methadone for opioid dependence both demonstrated increases in heroin-free days.
- There no statistical significance between the cost-effectiveness for buprenorphine and methadone.

[Doran et al., 2003]



Slide 26: Use of Buprenorphine: Studies on Cost-Effectiveness

Doran and colleagues (2003) conducted a clinical trial designed to assess the safety, efficacy and cost-effectiveness of buprenorphine versus methadone in the management of opioid dependence. The trial utilized a flexible dosing regime that was tailored to the clinical need of the patients, with high maximum doses, using the marketed tablet formulation, under double-blind conditions. A total of 405 subjects were randomized to a treatment at one of three specialist outpatient drug treatment centers in Adelaide and Sydney, Australia. The perspective of the cost-effectiveness analysis was that of the service provider and included costs relevant to the provision of treatment. The primary outcome measure used in the economic analysis was change in heroin-free days from baseline to the sixth month of treatment.

Key findings included:

- Both buprenorphine and methadone demonstrated increases in heroin-free days; and
- There was no statistical significance between the cost-effectiveness for buprenorphine and methadone.

Reference:

Doran, C. M., Shanahan, M., Mattick, R. P., Bell, J., White, J., & Ali, R. (2003). Buprenorphine versus methadone maintenance: A cost effectiveness analysis. *Drug and Alcohol Dependence*, 71(3): 29 –302.

Slide 26



<p>Use of Buprenorphine: Studies on Cost-Effectiveness, cont'</p> <ul style="list-style-type: none"> • Treatment with buprenorphine-naloxone was associated with a reduction in opioid utilization and cost in the first year of follow-up (Kaur & McQueen, 2008) • Systematic review found good studies supporting buprenorphine as a cost effective approach to opioid treatment (Doran, 2008) 	<p>Slide 27: Use of Buprenorphine: Studies on Cost-Effectiveness, cont'd</p> <p>Another study conducted by Kaur and McQueen (2008) found that the treatment with buprenorphine/naloxone was associated with a reduction in opioid utilization and cost in the first year of follow-up.</p> <p>Doran (2008) conducted a systematic review of the literature and found a number of studies supporting buprenorphine as a cost-effective approach to opioid treatment.</p> <p><u>References:</u></p> <p>Doran, C. M. (2008). Economic evaluation of interventions to treat opiate dependence: a review of the evidence. <i>Pharmacoeconomics</i>, 26(5), 371-393.</p> <p>Kaur, A. D., McQueen, A. & Jan, S. (2008). Opioid drug utilization and cost outcomes associated with the use of buprenorphine-naloxone in patients with a history of prescription opioid use. <i>Journal of Managed Care Pharmacy</i>, 14(2), 186-194.</p>	<p>Slide 27</p> 
<p>Use of Buprenorphine: Studies on Cost-Effectiveness, cont'</p> <ul style="list-style-type: none"> • Another study in Australia found buprenorphine demonstrated lower crime costs and higher quality adjusted life years (QALY), concluding the likelihood of net benefits from substituting buprenorphine for methadone. <p><small>(Harris, Gospodarevskaya, & Ritter, 2005)</small></p> 	<p>Slide 28: Use of Buprenorphine: Studies on Cost-Effectiveness, cont'd</p> <p>This study was the first to examine the cost effectiveness of buprenorphine as maintenance treatment for heroin dependence in a primary care setting. The study was a randomized, open-label, 12-month trial of 139 heroin-dependent patients in a community setting receiving individualized treatment regimens of buprenorphine or methadone. The study took a broad societal perspective and included health, crime and personal costs. The main outcomes were incremental cost per additional day free of heroin use and per the quality adjusted life years (QALY).</p> <p>The researchers found that buprenorphine demonstrated lower crime costs and higher quality adjusted life years.</p> <p><u>Reference:</u></p> <p>Harris, A. H., Gospodarevskaya, E., & Ritter, A. J. (2005). A randomised trial of the cost effectiveness of buprenorphine as an alternative to methadone maintenance treatment for heroin dependence in a primary care setting. <i>Pharmacoeconomics</i>, 23(1), 77-91.</p>	<p>Slide 28</p> 

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

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

Slide 29: What is the Ratio of Buprenorphine to Naloxone in the Combination Tablet

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).

Slide 29

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

Potency

Buprenorphine ≈ 2:1

Naloxone ≈ 15:1

(Chiang & Hawks, 2003)

Slide 30: 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 injected, the naloxone is the stronger medication and the antagonist effects dominate.

Reference:

Chiang, C.N., & Hawks, R.L. (2003). Pharmacokinetics of the combination tablet of buprenorphine and naloxone. *Drug and Alcohol Dependence*, 70, S39-S47.

Slide 30



Buprenorphine/Naloxone: What You Need to Know

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

Slide 31: Buprenorphine/Naloxone: What You Need to Know

- 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, meaning they bind strongly to the receptor site.

Additional Information for the Trainer(s):

Safety

Because of its ceiling effect and poor bioavailability, buprenorphine is safer in overdose than opioid full agonists. The maximal effects of buprenorphine appear to occur in the 16–32 mg dose range for sublingual tablets. Higher doses are unlikely to produce greater effects.

Respiratory depression from buprenorphine (or buprenorphine/ naloxone) overdose is less likely than from other opioids. There is no evidence of organ damage with chronic use of buprenorphine, but increases in liver enzymes are sometimes seen. There is no evidence of significant disruption of cognitive or psychomotor performance with buprenorphine maintenance dosing.

Side Effects

Side effects of buprenorphine are similar to those of other opioids and include nausea, vomiting, and constipation. Buprenorphine and buprenorphine/naloxone can precipitate the opioid withdrawal syndrome. Additionally, the withdrawal syndrome can be precipitated in individuals maintained on buprenorphine.

Slide 31



Clonidine

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

Slide 32: Clonidine

Clonidine (Catapres®; most often used to treat hypertension) has gained widespread recognition and acceptance for its usefulness as an agent for symptom suppression of opioid withdrawal.

Clonidine has some practical advantages for treating opioid withdrawal, including:

- It is not a scheduled medication.
- The use of opiates can be discontinued immediately in preparation for naltrexone induction or admission to a psychosocial treatment program.
- No special license is needed.
- It can be used in inpatient and outpatient settings; it is most effective when used in an inpatient setting as side effects can be monitored more closely.
- It partially suppresses peripheral symptoms of opiate withdrawal (e.g., nausea, vomiting, sweating, diarrhea), however, it is not effective at alleviating subjective effects of opiate withdrawal (e.g., general body aches, abdominal cramps, cravings, etc.).

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

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 no 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.

Slide 32

Contraindications 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 33: 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, and history of fainting or dizziness on rising.

Clonidine is in Category C for pregnancy. This means that there is not enough information to determine if it is safe for use in pregnant women.

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). Examples of CNS depressants include 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 33

Medically – Assisted Withdrawal
(a.k.a. Dose Tapering; a.k.a. Detoxification)

**Slide 34: 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. Detoxification from opiate dependence most often involves the administration of an opiate agonist (e.g., methadone) or the non-opiate clonidine (Fishbain, Rosomoff, & Cutler, 1993; Valmana, 1999).

Withdrawing from opioids is often 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 opioids and may need to continue receiving their medication for an extended period. Unstable living situations, multiple relapses, previous failed detoxification attempts, or lack of desire to withdraw from opioids, may indicate that medication maintenance is a better treatment option.

References:

Fishbain, D. A., Rosomoff, H. L., & Cutler, R. (1993). Opiate detoxification protocols. A clinical manual. *Annals of Clinical Psychiatry*, 5(1), 53–65.

Valmana, A. (1999). Non-methadone pharmacotherapies in opioid addiction. *Current Opinion in Psychiatry*, 12(3), 307-310.

Slide 34



Withdrawal

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

OR

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

Slide 35: 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 (Center for Substance Abuse Treatment, 2006). In this training, we will refer to this as an **opioid taper**.

References:

Alling, F. A. (1992). Detoxification and treatment of acute sequelae. In J.H. Lowinson, P. Ruiz, R.B. Millman & J.G. Langrod (Eds.), *Substance abuse: A comprehensive textbook* (second edition), (pp. 402-415). Baltimore: Williams & Wilkins.

Center for Substance Abuse Treatment. *Detoxification and Substance Abuse Treatment*. Treatment Improvement Protocol (TIP) Series 45. DHHS Publication No. (SMA) 06-4131. Rockville, MD: Substance Abuse and Mental Health Services Administration, 2006.

Slide 35



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 36: 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 of the drug used. Opioids with short half-lives (e.g., heroin) have acute withdrawal symptoms that peak at days 3-4 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.

Slide 36

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

(NIDA, 2006)

Slide 37: Medically- Assisted Withdrawal

The individual is systematically withdrawn from addicting drugs. Medications (e.g., methadone, buprenorphine, and 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.

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

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.

Slide 37

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 38: Principles of Medically-Assisted Withdrawal

Slide 38

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

Because there is a risk of serious adverse consequences for some patients who undergo withdrawal, an initial assessment should be conducted that includes 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); and the medical and psychiatric history.

- Strategies for pharmacologic management of withdrawal:
- (1) suppression of withdrawal by transitioning the patient onto a long-acting opioid (e.g., buprenorphine or methadone) and then tapering the medication over a period of time);
 - (2) decreasing signs and symptoms of withdrawal (i.e., use of ancillary medications to treat symptoms).

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

The appropriate level of care following withdrawal is 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.

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.

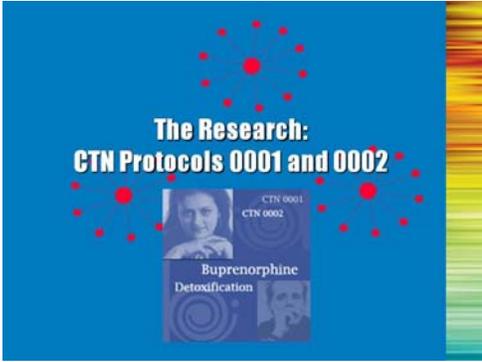
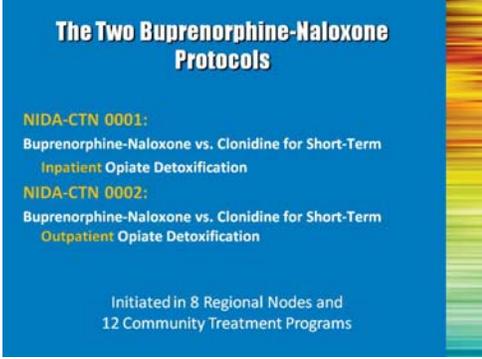
Slide 39: Why the Focus on Medically-Assisted Withdrawal (Detoxification)?

Slide 39

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 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.

	<p>Slide 40: The Research: CTN Protocols 0001 and 0002 (Transition Slide)</p> <p>This package of materials is based on research conducted through the CTN.</p> <p>For the first studies conducted by the CTN, NIDA chose to compare a standard treatment for helping patients taper from opioids (clonidine) to a new treatment (buprenorphine). Two clinical trials were developed and implemented to compare these medications.</p> <p><u>Reference:</u></p> <p>Ling, W., Amass, L., Shoptaw, S., Annon, J. J., Hillhouse, M., Babcock, D., et al. (2005). A multi-center randomized trial of buprenorphine-naloxone versus clonidine for opioid detoxification: Findings from the National Institute on Drug Abuse Clinical Trials Network. <i>Addiction</i>, 100, 1090-1100.</p>	<p>Slide 40</p> 
	<p>Slide 41: The Two Buprenorphine-Naloxone Protocols</p> <p>The studies were identical, except for 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.</p>	<p>Slide 41</p>
	<p>Slide 42: Site Participation NIDA-CTN 0001</p> <p>Overall, the studies were conducted in eight Regional Nodes and 12 Community Treatment Programs</p> <p>For the inpatient protocol, six sites in five regional nodes across the country participated in the study.</p>	<p>Slide 42</p>

<p>Site Participation NIDA-CTN 0002</p>	<p>Slide 43: Site Participation NIDA-CTN 0002</p> <p>For the outpatient protocol, six sites in five nodes participated in the study.</p>	<p>Slide 43</p>
<p>NIDA CTN 0001/0002 Buprenorphine-Naloxone Detoxification Protocols</p> <ul style="list-style-type: none"> • 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 	<p>Slide 44: NIDA CTN 0001/0002 Buprenorphine Naloxone Detoxification Protocols</p> <p>As information is being gathered to determine whether or not a medication is effective for treatment of a particular problem, the studies are usually <i>blinded</i>. This means that the patients (and usually the researcher) do not know if a particular patient is taking the active medication or a placebo/other medication. 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 (or placebo) from positively or negatively influencing the results.</p> <p>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 <i>open-label studies</i>—both patients and researchers know what they are taking—which was the case in these studies.</p> <p>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.</p>	<p>Slide 44</p>

Community Treatment Programs	
<p>6 Inpatient</p> <ul style="list-style-type: none"> 2 Therapeutic Communities 1 Free-standing, Chemical Dependency Hospital 2 Detox Units with Integrated Addiction and Mental Health Services 1 Long Term Residential <p><u>Usual care approaches:</u> 50% methadone, 50% clonidine</p>	<p>6 Outpatient</p> <ul style="list-style-type: none"> 4 Opioid Treatment Programs 1 HMO 1 Community Mental Health Center <p><u>Usual care approaches:</u> methadone in OTPs and clonidine in HMO</p>

Slide 45: Community Treatment Programs

Slide 45

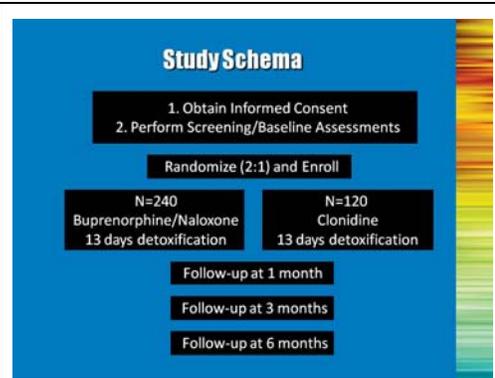
There was considerable variability in several areas in both the inpatient and outpatient programs. CTP and physicians' experience with opioid users and narcotic treatment medications varied. Nine of the 12 physicians participating were certified by the American Society for Addiction Medicine; all actively treated substance abusers; training backgrounds included addiction psychiatry, internal or family medicine, pediatrics or anesthesiology; and professional experience ranged from 1 to 20 years.

The majority of the participating programs were based in urban settings, with only one located in a more rural setting. Nine of the 12 programs were public non-profit; one program was public for-profit; and one program was private for-profit.

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 detoxification with methadone and half with clonidine. In outpatient, four of the six programs were methadone programs and used methadone, the other two 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.



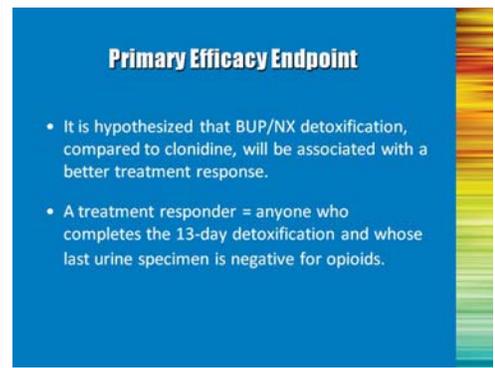
Slide 46: Study Schema

Slide 46

The goal of CTN 0001 and 0002 was to compare the efficacy of these two medications for short-term opioid withdrawal. The 2-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 according to a predetermined schedule on each day of the taper. Ancillary medications 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 2:1 ratio to buprenorphine or clonidine. Participants received medication and evaluation for 13 days and then were followed up at 1, 3 and 6 months.



Slide 47: Primary Efficacy Endpoint

Slide 47

The researchers conducting this study were testing the hypothesis that buprenorphine would be associated with better treatment response compared to clonidine To test this hypothesis, 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).

Note to the Trainer(s): *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.

Slide 48

Demographics 0001 (Inpatient)

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

Slide 49: Demographics 0001 (Inpatient)

Demographics were similar across the two groups. They were:

- Predominantly male;
- Predominantly white, but with representation from other ethnic minority groups.
- Participants were in their mid-30s.
- Two-thirds were employed.
- They had been using heroin for about 6.5 years at the time they began the study.

Slide 49

Present and Opioid Negative 0001 (Inpatient)

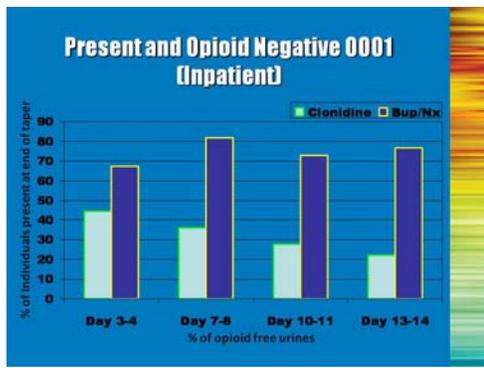
Present and opioid neg	Bup/Nx (N)	%	Clonidine (N)	%
N	77		36	
Day 3 or 4	52	67.5	16	44.4
Day 7 or 8	63	81.8	13	36.1
Day 10 or 11	56	72.7	10	27.8
Day 13 or 14	59	76.6	8	22.2

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 not directly observed, but monitored using temperature testing. The data presented in the slides at this point pertains specifically to opioid-free urines.

Among the participants in the inpatient study, $\frac{3}{4}$ of participants were present 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.

Slide 50



Slide 51: Present and Opioid Negative 0001 (Inpatient)

Slide 51

This slide shows the same information graphically. At the end of the withdrawal, buprenorphine was 3.4 times more effective than clonidine in helping people to be present and opioid negative.

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

Slide 52: Demographics 0002 (Outpatient)

Slide 52

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 than those in the inpatient study (9.4 vs. 6.6 years).

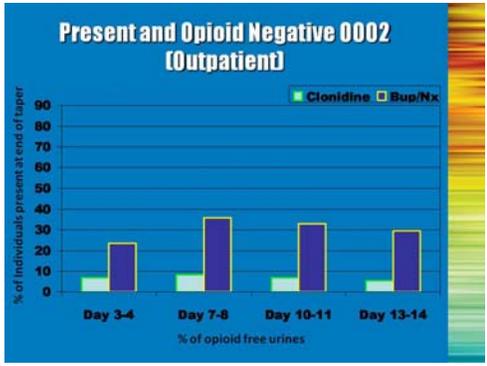
Present and opioid neg	Bup/Nx (N)	%	Clonidine (N)	%
N	157		74	
Day 3 or 4	37	23.6	5	6.8
Day 7 or 8	56	35.7	6	8.1
Day 10 or 11	52	33.1	5	6.8
Day 13 or 14	46	29.3	4	5.4

Slide 53: Present and Opioid Negative 0002 (Outpatient)

Slide 53

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 one in three participants receiving buprenorphine were present and provided an opioid negative urine sample. In the clonidine group, only one in 20 participants were present and opioid free.



Slide 54: Present and Opioid Negative 0002 (Outpatient)

Again, this slide shows the same information graphically. At the end of the withdrawal, buprenorphine was 5.4 times more effective than clonidine in helping people to be present and opioid negative.

Slide 54

NNT: Number Needed to Treat

CTN 0001 (Inpatient)

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

NNT Clonidine: BupNx = 3.44

CTN 0002 (Outpatient)

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

NNT Clonidine: Bup/Nx = 5.44

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

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 defined 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 patients, which 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 is 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.

Slide 55



<p style="text-align: center;">Protocol</p> <p>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</p>	<p>Slide 56: Protocol</p> <p>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.</p> <p>The three main objectives of the program were:</p> <ul style="list-style-type: none"> • Improved 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. 	<p>Slide 56</p>
<p style="text-align: center;">The results of the protocols were pretty dramatic...</p>	<p>Slide 57: The results of the protocol were pretty dramatic</p> <p>In summary, the result of this protocol supports the use of buprenorphine for this 13-day taper schedule.</p>	<p>Slide 57</p>
<p style="text-align: center;">Outcomes</p> <ul style="list-style-type: none"> • The taper was successful in both outpatient and inpatient settings • Buprenorphine/naloxone was superior to clonidine in both settings • Inpatient setting: 76% of buprenorphine/naloxone patients vs. 22% of clonidine patients present and opioid clean at day 13 • Outpatient setting: 29% of buprenorphine/ naloxone patients vs. 5% of clonidine patients present and opioid clean at day 13 	<p>Slide 58: Outcomes</p> <p>A 13-day taper, utilizing a prescribed schedule, demonstrated the following results:</p> <ul style="list-style-type: none"> • The taper using buprenorphine 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. 	<p>Slide 58</p>

<p>...so if I want to do this, what steps do I take?</p>	<p>Slide 59: So if I want to do this, what steps do I take? (Transition slide)</p> <p><i>Read text</i></p>	<p>Slide 59</p>
<p>First, the patient must be screened for appropriateness for buprenorphine treatment</p>	<p>Slide 60: First, the patient must be screened for appropriateness for buprenorphine treatment</p> <p>Most patients can be considered for treatment with buprenorphine provided they are opioid dependent and interested in medication-assisted withdrawal.</p>	<p>Slide 60</p>

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 (Addiction Severity Inventory Lite);
- DSM-IV checklist for substance dependence;
- HIV risk assessment; and
- 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 should be observed for symptoms of precipitated opioid withdrawal.

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

Slide 61

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 conducted with each patient and included:

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

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 patient could be randomized to receive clonidine, which, as previously discussed, has 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.

Additional Note for the Trainer(s): *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 shown that buprenorphine passes into the mother’s milk. Breast-feeding is therefore not advised in mothers treated with Suboxone®.*

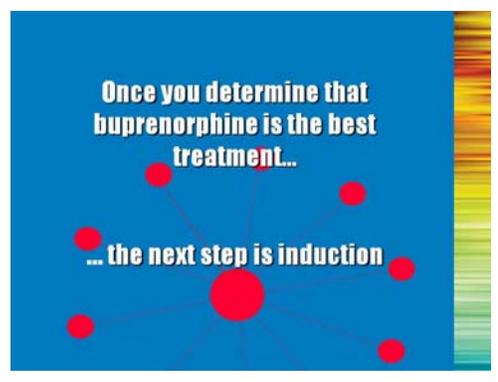
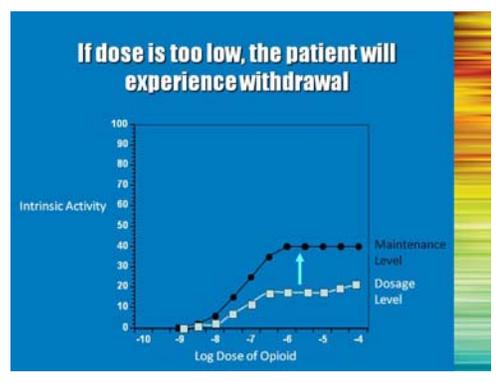
Additional Information for the Trainer(s): *Jones, et al. (2005) conducted a study of pregnant women who enrolled during their second trimester. The only statistically significant finding is that women receiving buprenorphine required shorter hospital stays than women on methadone. Trends indicated that fewer infants needed to be treated for Neonatal Abstinence Syndrome (NAS) and that less NAS medications were needed when treated with buprenorphine compared with methadone. A multi-site replication trial is now underway.*

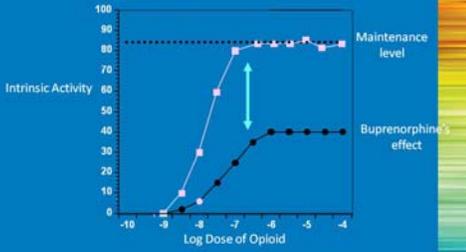
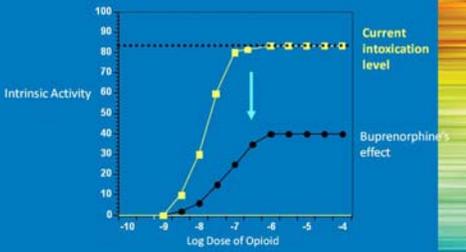
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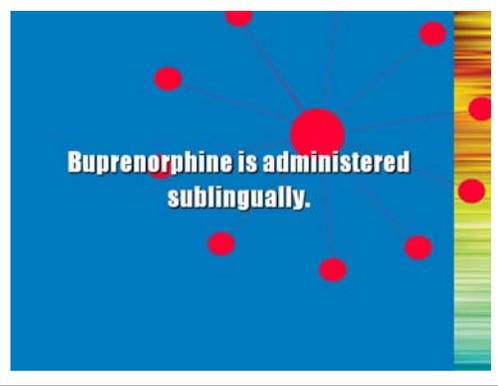
Jones, H. E., Johnson, R. E., Jasinski, D. R., O’Grady, K. E., Chisholm, C. A., Choo, R. E., et al. (2005). Buprenorphine versus methadone in the treatment of pregnant opioid-dependent patients: Effects on the neonatal abstinence syndrome. *Drug and Alcohol Dependence*, 79, 1-10.

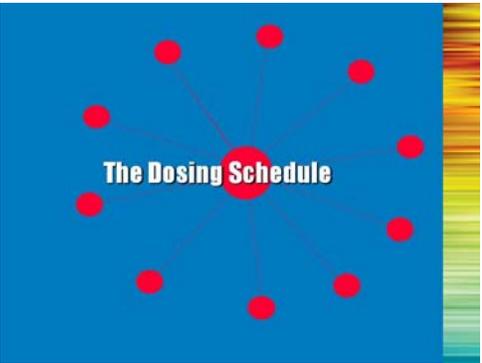
Slide 62



<p>Once you determine that buprenorphine is the best treatment...</p> <p>... the next step is induction</p> 	<p>Slide 63: Once you determine that buprenorphine is the best treatment...the next step is induction</p> <p>Starting the patient on the medication is pretty straightforward, 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.</p>	<p>Slide 63</p>																								
<p>Transferring Patients Onto Buprenorphine: 3 Ways Significant Withdrawal Could Occur</p> <p>Dose too low?</p> <p>Insufficient agonist effects</p> 	<p>Slide 64: Transferring Patients Onto Buprenorphine: 3 Ways Significant Withdrawal Could Occur</p> <p>There are three ways that a patient can experience withdrawal symptoms.</p> <p>First, if an insufficient dose of buprenorphine is given, the person may experience withdrawal from being under medicated.</p>	<p>Slide 64</p>																								
<p>If dose is too low, the patient will experience withdrawal</p>  <table border="1"> <caption>Graph Data: Intrinsic Activity vs Log Dose of Opioid</caption> <thead> <tr> <th>Log Dose of Opioid</th> <th>Maintenance Level (Green)</th> <th>Dosage Level (White)</th> </tr> </thead> <tbody> <tr><td>-10</td><td>0</td><td>0</td></tr> <tr><td>-9</td><td>0</td><td>0</td></tr> <tr><td>-8</td><td>10</td><td>5</td></tr> <tr><td>-7</td><td>30</td><td>15</td></tr> <tr><td>-6</td><td>40</td><td>20</td></tr> <tr><td>-5</td><td>40</td><td>20</td></tr> <tr><td>-4</td><td>40</td><td>20</td></tr> </tbody> </table>	Log Dose of Opioid	Maintenance Level (Green)	Dosage Level (White)	-10	0	0	-9	0	0	-8	10	5	-7	30	15	-6	40	20	-5	40	20	-4	40	20	<p>Slide 65: If dose is too low, the patient will experience withdrawal</p> <p>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.</p>	<p>Slide 65</p>
Log Dose of Opioid	Maintenance Level (Green)	Dosage Level (White)																								
-10	0	0																								
-9	0	0																								
-8	10	5																								
-7	30	15																								
-6	40	20																								
-5	40	20																								
-4	40	20																								
<p>Transferring Patients Onto Buprenorphine: 3 Ways Significant Withdrawal Could Occur</p> <p>Dose too low?</p> <p>Insufficient agonist effects</p> <p>Not full agonist</p> <p>May not fully replace</p> 	<p>Slide 66: Transferring Patients Onto Buprenorphine: 3 Ways Significant Withdrawal Could Occur</p> <p>A second way that a person can experience withdrawal has to do with the properties of buprenorphine itself—the ceiling effect.</p>	<p>Slide 66</p>																								

<p>If the patient needs a high level of medication to achieve maintenance, the ceiling effect of buprenorphine may result in withdrawal</p> 	<p>Slide 67: If the patient needs a high level of medication to achieve maintenance, the ceiling effect of buprenorphine may result in withdrawal</p> <p>As described before, as the dose of buprenorphine increases, the agonist effects level off. For someone who is dependent on very high doses of opioids, they may need an effect greater than can be achieved with buprenorphine in order to not feel sick.</p> <p>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 level of drug use before switching to buprenorphine. This can be done in a structured opioid treatment program, and should not be attempted with someone using illicit opioids.</p>	<p>Slide 67</p>
<p>Transferring Patients Onto Buprenorphine: 3 Ways Significant Withdrawal Could Occur</p> <ul style="list-style-type: none"> Dose too low? <ul style="list-style-type: none"> Insufficient agonist effects Not full agonist <ul style="list-style-type: none"> May not fully replace Precipitates Withdrawal <ul style="list-style-type: none"> Ceiling effect 	<p>Slide 68: Transferring Patients Onto Buprenorphine: 3 Ways Significant Withdrawal Could Occur</p> <p>Finally, there is precipitated withdrawal. This also has to do with the ceiling effect and receptor affinity.</p>	<p>Slide 68</p>
<p>Buprenorphine will replace other opioids at the receptor site; therefore, the patient experiences withdrawal.</p> 	<p>Slide 69: Buprenorphine will replace other opioids at the receptor site; therefore, the patient experiences withdrawal.</p> <p>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, it's as if the level of opioids in the system has suddenly decreased, and the patient will experience this as withdrawal.</p> <p>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.</p>	<p>Slide 69</p>

 <p>Buprenorphine is administered sublingually.</p>	<p>Slide 70: Buprenorphine is administered sublingually.</p> <p>The sublingual tablet should be held under the tongue until dissolved, which can take 2 to 10 minutes.</p> <p>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.</p>	<p>Slide 70</p>
 <p>What will the tablets look like? How will they taste?</p> <ul style="list-style-type: none"> • 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. 	<p>Slide 71: What will the tablets look like? How will they taste?</p> <p>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.</p> <p>The tablets are orange and have a citrus flavor to mask the bitter taste experienced by some people.</p>	<p>Slide 71</p>

<p>Five Steps to Starting Bup/Nx</p> <ol style="list-style-type: none"> 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 	<p>Slide 72: Five Steps to Starting Bup/Nx</p> <p>There are five recommended steps for initiating treatment with buprenorphine.</p> <p>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.</p> <p>Mild withdrawal can be evaluated based on clinical signs. Using a structured instrument 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.</p> <p><u>Clinical Opiate Withdrawal Scale (COWS)</u>. 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.</p> <p><u>Reference:</u> Wesson, D. R., & Ling, W. (2003). The Clinical Opiate Withdrawal Scale (COWS). <i>Journal of Psychoactive Drugs</i>, 35, 253-259.</p>	<p>Slide 72</p> 
<p>The Dosing Schedule</p> 	<p>Slide 73: The Dosing Schedule</p> <p>The dosing schedule for this taper was uniform for everyone. This was necessary for research purposes. Additionally, the dosing schedule has the benefit of ensuring that people are brought onto buprenorphine as quickly as possible, and then tapered off over as long as possible.</p> <p>The specific dosing schedule is as follows:</p>	<p>Slide 73</p>

Day 1 Dose Induction

	Day 1	Day 2	Day 3
Bup-Nx DOSE	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 received 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 to 16 mg. After day 3, the tapering of the medication began with decreasing dosages.

Slide 74

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

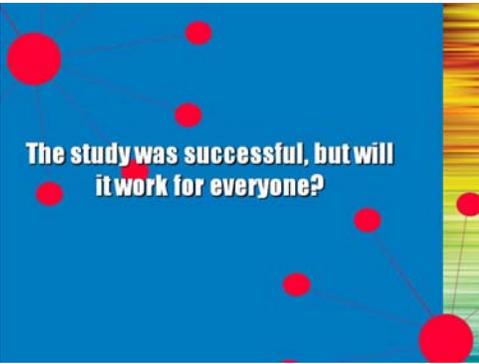
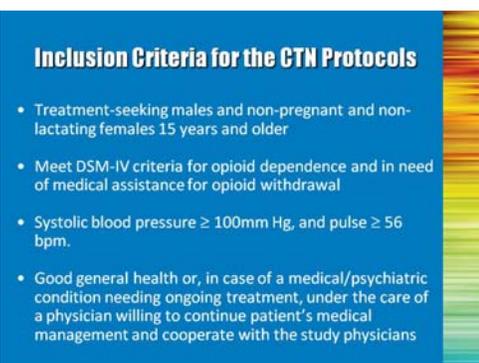
Slide 75: BUP-NX Taper Schedule

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 patients dropped out between day 3 and 4. This is not surprising given that this is when the withdrawal symptoms would be most severe.

Slide 75

 <p>The study was successful, but will it work for everyone?</p>	<p>Slide 76: The study was successful, but will it work for everyone?</p> <p>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.</p>	<p>Slide 76</p>
 <p>Inclusion Criteria for the CTN Protocols</p> <ul style="list-style-type: none"> • 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 	<p>Slide 77: Inclusion Criteria for the CTN Protocols</p> <p>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.</p> <ul style="list-style-type: none"> • Both buprenorphine and clonidine are labeled as Category C for pregnancy. <p>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.</p> <p>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.</p> <ul style="list-style-type: none"> • 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. <p>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.</p>	<p>Slide 77</p>

<p style="text-align: center;">Inclusion Criteria for the CTN Protocols, cont'</p> <ul style="list-style-type: none"> • 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: <ul style="list-style-type: none"> - 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 	<p>Slide 78: Inclusion Criteria for the CTN Protocols, cont'd</p> <p>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 them, including the details about the study, such as its purpose, duration, required procedures, key contacts, risks and potential benefits. The participant then decides whether or not to participate in the study. Minors cannot legally sign consent, so a parent or legal guardian would need to consent for them.</p> <p>Due to the concerns about pregnancy with these medications, use of an acceptable form of birth control was required from female participants.</p>	<p style="text-align: center;">Slide 78</p>
<p style="text-align: center;">Exclusion Criteria for the CTN Protocols</p> <ul style="list-style-type: none"> • 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 	<p>Slide 79: Exclusion Criteria for the CTN Protocols</p> <p>Clients were excluded from participation in the trial if they met any of these exclusion criteria:</p> <ul style="list-style-type: none"> • If the person was found to have a significant medical conditions thought to potentially 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 was asked to evaluate to determine if the finding was clinically significant. • Known allergy or sensitivity to any of the study medications would indicate that it is not an appropriate option for treatment. In the case of a research study, where the physician and the patient get no choice as to which medication the patient receives 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. <p>Severe psychiatric issues or suicidal risk would exclude the person as they need to be stabilized urgently and then treatment of other conditions considered.</p>	<p style="text-align: center;">Slide 79</p>

<p style="text-align: center;">Exclusion Criteria for the CTN Protocols, cont'</p> <ul style="list-style-type: none"> • 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 	<p>Slide 80: Exclusion Criteria for the CTN Protocols , cont'd</p> <ul style="list-style-type: none"> • 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 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. 	<p>Slide 80</p>
<p style="text-align: center;">Ancillary Medications for Treatment of Withdrawal Symptoms</p> 	<p>Slide 81: Ancillary Medications for Treatment of Withdrawal Symptoms (Transition Slide)</p>	<p>Slide 81</p>
<p style="text-align: center;">Ancillary Medications</p> <ul style="list-style-type: none"> • 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 	<p>Slide 82: Ancillary Medications</p> <p>The use of ancillary medication during opioid withdrawal is fairly common, especially when using non-narcotic agents such as clonidine.</p> <p>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.</p> <p>Most patients received at least one ancillary medication during the study.</p>	<p>Slide 82</p>

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 choices 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 medically-assisted withdrawal, patients were given instructions regarding the use of the medication. Refills were made available to all participants during each scheduled clinic visit.

Slide 83

<p style="text-align: center;">Ancillary Medications Used in the CTN Protocols</p> <p>Bone Pain and Arthralgias</p> <ul style="list-style-type: none"> • Acetaminophen 650 mg q 4-6 NTE 3900 in 24 hrs. • Ibuprofen 800 mg q 8 w/food • Methocarbamol (Robaxin) 500-1000 mg q6 hrs prn; NTE 2000 mg per 24 hrs. <p>Diarrhea</p> <ul style="list-style-type: none"> • Loperamide (Immodium) 2mg; NTE 8mg per 24 hrs. • Donnatal 1-2 tablets q 6-8 hrs prn; NTE 8 tablets per 24 hrs. 	<p>Slide 84: Ancillary Medications Used in CTN Protocols</p> <p>Following are the withdrawal symptoms and the medications that were available to treat them:</p> <p>Bone pain and Arthralgias</p> <ul style="list-style-type: none"> • Acetaminophen (650 mg q 4-6 hrs; NTE 3900 mg per 24 hrs) • Ibuprofen (800 mg q 8 hrs with food) • Methocarbamol (Robaxin) (500-1000 mg q 6 hrs prn; NTE 2000 mg per 24 hrs) <p>Diarrhea</p> <ul style="list-style-type: none"> • Loperamide (Immodium) (2 mg; NTE 8 mg per 24 hrs) • Donnatal (1-2 tablets q 6-8 hrs prn; NTE 8 tablets per 24 hrs) 	<p>Slide 84</p>
<p style="text-align: center;">Ancillary Medications Used in the CTN Protocols</p> <p>Anxiety and Restlessness (use one of the following)</p> <ul style="list-style-type: none"> • Lorazepam (Ativan) 1-2 mg q 6 hrs. prn; NTE 8 mg per 24 hrs. • Oxazepam (Serax) 15 - 30 mg po q 6 hrs. prn; NTE 120 mg per 24 hrs. • Phenobarbital 15 - 30 mg po q 6 hrs. prn; NTE 120 mg per 24 hrs. • Hydroxyzine hydrochloride (Atarax/Vistaril) 50 mg, po q 6 hrs. prn; NTE 200 mg per 24 hrs. 	<p>Slide 85: Ancillary Medications Used in CTN Protocols</p> <p>Anxiety and Restlessness</p> <ul style="list-style-type: none"> • Lorazepam (1-2 mg q 6 hrs prn; NTE 8 mg per 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 24hrs) • Hydroxyzine hydrochloride (50 mg, po q 6 hrs prn; NTE 200 mg per 24 hrs) <p>Physicians prescribing the medications were aware of the cautions related to over use of benzodiazepines; 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.</p>	<p>Slide 85</p>

Ancillary Medications Used in the CTN Protocols

Nausea

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

Insomnia

- Diphenhydramine (Benadryl) 25-50mg; NTE 300mg per 24 hrs.
- Zolpidem Tartrate (Ambien) 10mg, 1-3 tabs, po q hs prn
- Trazadone Hydrochloride (Desyrel) 50mg, 1 to 3 tabs, po q hs prn
- Doxepin Hydrochloride (Sinequan) 50mg, 1 to 3 tabs, po q hs prn

Slide 86: Ancillary Medications Used in CTN Protocols

Nausea

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

Insomnia

- **Diphenhydramine (Benadryl)** (25-50 mg; NTE 300 mg per 24 hrs)
- **Zolpidem Tartrate (Ambien)** (10 mg, 1-3 tabs, po q hs prn)
- **Trazadone Hydrochloride** (50 mg, 1-3 tabs, po q hs prn)
- **Doxepin Hydrochloride** (50 mg, 1-3 tabs, po q hs prn)

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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 & Arthralgias	Anxiety & Restlessness	Nausea	Diarrhea
62%	54%	52%	35%	25%

- Average of 2.3 withdrawal symptoms were treated

(Amass et al., 2004)

Slide 87: Ancillary Medications Used Among Patients Receiving Buprenorphine

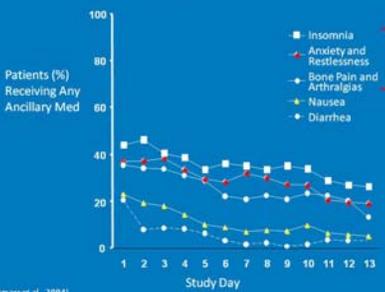
Slide 87

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

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

The most common symptoms treated were **insomnia** (most commonly treated with zolpidem tartrate [Ambien] or trazadone), **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).

Ancillary Medication Use



(Amass et al., 2004)

Slide 88: Ancillary Medication Use

Slide 88

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.

<p>Adverse Events</p> <p>That is, what additional symptoms did patients report?</p>	<p>Slide 89: Adverse Events</p> <p>Patients reported additional symptoms or problems during the taper. These are defined in research protocols as adverse events.</p>	<p>Slide 89</p>
<p>Adverse Events</p> <ul style="list-style-type: none"> • 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. 	<p>Slide 90: Adverse Events</p> <p>Information about adverse events is collected in all medically-related research studies.</p> <p>Adverse events are defined as any untoward medical or psychiatric occurrence during the patient's participation in the trial.</p> <p>Adverse events may or may not be related to the treatment being provided.</p> <p>By collecting adverse event information, data concerning side effects of the treatment is obtained.</p>	<p>Slide 90</p>

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)
(For additional information, refer to Slide #72)
- Adjective Rating Scale for Withdrawal (ARSW)
- Visual Analog Scale (VAS)

Adjective Rating Scale for Withdrawal (ARSW). The ARSW is comprised of 16 signs and symptoms of opioid withdrawal (Bickel, Stitzer, Bigelow, et al., 1988; Bickel, Stitzer, Liebson & Bigelow, 1988; 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 Scale (VAS). This scale consists of a 100-point line anchored with “not at all” on one end (0) and “extremely” on the other (100).

References:

Bickel, W. K., Stitzer, M. L., Bigelow, G. E., Liebson, I.A., Jasinski, D. E., & Johnson, R. E. (1988). Buprenorphine: dose-related blockade of opioid challenge effects in opioid dependent humans. *Journal of Pharmacology and Experimental Therapeutics*, 247, 47-53.

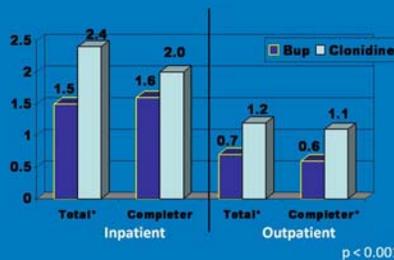
Bickel, W. K., Stitzer, M. L., Liebson, I A., & Bigelow, G. E. (1988). Acute physical dependence in man: effects of naloxone after brief morphine exposure. *Journal of Pharmacology and Experimental Therapeutics*, 244, 126-132.

Amass, L., Kamien, J. B., & Idulich, S.K. (2000). Efficacy of daily and alternate-day dosing regimens with the combination buprenorphine–naloxone tablet. *Drug and Alcohol Dependence*, 58, 143-153.

Slide 91



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 differences were seen in the number of events reported for the total sample but not for those completing the taper. In the outpatient study, differences were seen in both the total sample and completers.

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 they 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.

Slide 92

BUP/NX Safety Profile was Excellent

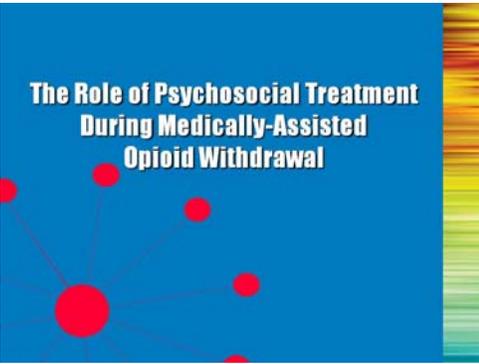
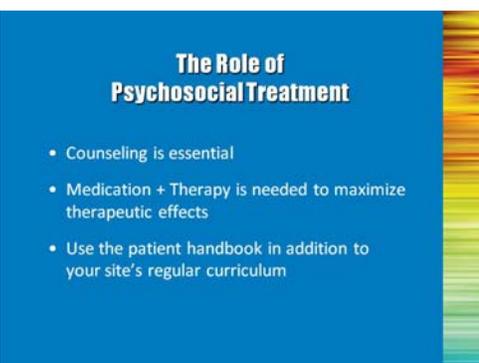
- Eighteen individuals experienced serious side effects over the course of the clinical trial:
 - 61% were associated with hospitalization for drug relapse or similarly related treatment
 - 83% transpired during the follow-up period
 - One death in the buprenorphine condition was secondary to respiratory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

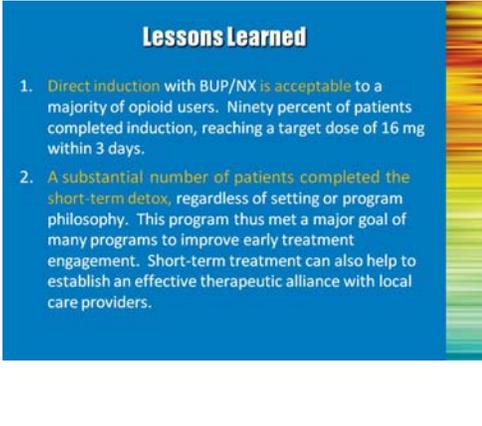
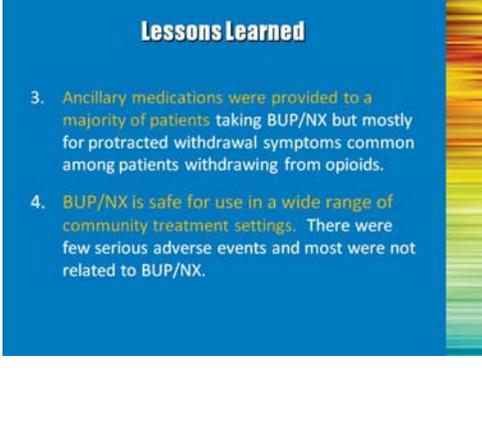
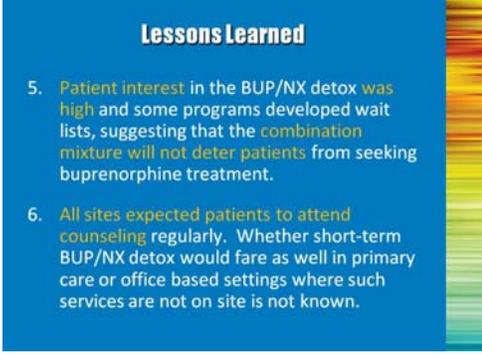
Slide 93: BUP/NX Safety Profile was Excellent

Eighteen side effects were reported over the course of the 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—may have been study-related; 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.

Slide 93

 <p>The Role of Psychosocial Treatment During Medically-Assisted Opioid Withdrawal</p>	<p>Slide 94: The Role of Psychosocial Treatment During Medically-Assisted Opioid Withdrawal</p> <p>The 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 settings and participants received psychosocial treatment as provided by the treatment agency.</p>	<p>Slide 94</p>
 <p>The Role of Psychosocial Treatment</p> <ul style="list-style-type: none"> • Counseling is essential • Medication + Therapy is needed to maximize therapeutic effects • Use the patient handbook in addition to your site's regular curriculum 	<p>Slide 95: The Role of Psychosocial Treatment</p> <p>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.</p> <p>Note to the Trainer(s): 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.</p> <p>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 and data were not collected about this.</p> <p>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.</p> <p>This speaks well for the treatment across settings. However, additional research is needed to determine what type of psychosocial 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.</p>	<p>Slide 95</p> 

 <p>Key Lessons Learned from the CTN Experience</p>	<p>Slide 96: Key Lessons Learned from the CTN Experience (Transition Slide)</p> <p>In summary, let's look at the lessons that were learned from Implementing this taper schedule in diverse inpatient and outpatient settings across the country.</p>	<p>Slide 96</p>
 <p>Lessons Learned</p> <ol style="list-style-type: none"> 1. Direct induction with BUP/NX is acceptable to a majority of opioid users. Ninety percent of patients completed induction, reaching a target dose of 16 mg within 3 days. 2. A substantial number of patients completed the short-term detox, regardless of setting or program philosophy. This program thus met a major goal of many programs to improve early treatment engagement. Short-term treatment can also help to establish an effective therapeutic alliance with local care providers. 	<p>Slide 97: Lessons Learned</p> <p>(1) First, the medication was acceptable to the people taking it. Ninety percent (90%) of the participants in the buprenorphine group were successfully inducted onto the medication. That is, they received the first three doses and reached 16 mg.</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>Slide 97</p>
 <p>Lessons Learned</p> <ol style="list-style-type: none"> 3. Ancillary medications were provided to a majority of patients taking BUP/NX but mostly for protracted withdrawal symptoms common among patients withdrawing from opioids. 4. BUP/NX is safe for use in a wide range of community treatment settings. There were few serious adverse events and most were not related to BUP/NX. 	<p>Slide 98: Lessons Learned</p> <p>(3) While the majority of participants experienced some negative symptoms that required use of an ancillary medication, generally, these were symptoms that are commonly seen during opioid withdrawal and not a negative effect of the medication.</p> <p>(4) There were few serious adverse events in the trial and only one <i>may</i> have been related to the medication. This indicates that buprenorphine is safe for use in these treatment settings.</p>	<p>Slide 98</p>
 <p>Lessons Learned</p> <ol style="list-style-type: none"> 5. Patient interest in the BUP/NX detox was high and some programs developed wait lists, suggesting that the combination mixture will not deter patients from seeking buprenorphine treatment. 6. All sites expected patients to attend counseling regularly. Whether short-term BUP/NX detox would fare as well in primary care or office based settings where such services are not on site is not known. 	<p>Slide 99: Lessons Learned</p> <p>There is considerable interest in 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 the acceptance of the medication among the target group for treatment.</p>	<p>Slide 99</p>

Lessons from Additional Analyses: Predictors of Treatment Success

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

(Ziedonis et al., 2009)

Slide 100: Lessons from Additional Analyses: Predictors of Treatment Success

Ziedonis and his colleagues (2009) did additional analysis of data from this study to determine predictors of treatment success (i.e., being present and opioid free at the end of the taper).

Predictors include:

- Type of medication (buprenorphine)
- Treatment setting (inpatient)
- Degree of reduction in withdrawal symptoms in first 3 days of treatment (greater reduction)

Additionally, those in the clonidine group with better outcomes had lower withdrawal symptoms at baseline.

Reference:

Ziedonis, D. M., Amass, L., Steinberg, M., Woody, G., Krejci, J., Annon, J. J., et al. (2009). Predictors of outcome for short-term medically supervised opioid withdrawal during a randomized, multicenter trial of buprenorphine-naloxone and clonidine in the NIDA clinical trials network drug and alcohol dependence. *Drug and Alcohol Dependence*, 99, 28-36.

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Lessons from a Study of Longer and Shorter Taper Schedules

- Differences in being drug free at end taper did not differ for 7 or 28 day groups (after 4 week stabilization)
- A relatively quick taper may be advantageous and did not result in relapse to drug use at greater rates than longer tapers
- Patients stabilized physiologically on a range of buprenorphine doses can be tapered successfully over 7 days
- There was no advantage to prolonging the tapering schedule for weeks

(Ling et al., 2009)

Slide 101: Lessons from a Study of Longer and Shorter Taper Schedules

Ling and his colleagues (2009) conducted a follow-up trial in which all participants were stabilized for 4 weeks and then randomized to a 7- or 28- day taper.

Results of this study showed no difference in treatment success between the groups. The authors concluded that:

- A relatively quick taper may be advantageous and did not result in relapse to drug use at greater rates than a longer taper.
- Patients stabilized physiologically on a range of buprenorphine doses can be tapered successfully over 7 days.
- For patients who are stabilized, there was no advantage to prolonging the tapering schedule for weeks.

Reference:

Ling, W., Hillhouse, M., Domier, C., Doraimani, G., Hunter, J., Thomas, C., et al. (2009). Buprenorphine tapering schedule and illicit opioid use. *Addiction*, 104, 256-265.

Slide
101



<p>Additional Research</p> <p>More research is needed to answer questions such as:</p> <ul style="list-style-type: none"> • To what degree do these patients <i>return to opioid use</i> following taper? • What <i>counseling is best</i> coupled with this taper? • What <i>difference would it make if the treatment were provided in a physician's office</i> rather than in a substance abuse treatment program or clinic where other ancillary services are available? 	<p>Slide 102: Additional Research</p> <p>Additional research is needed to determine:</p> <ul style="list-style-type: none"> • To what degree do these patients return to opioid use following taper? • What counseling is best coupled with this taper? • What difference would it make if the treatment were provided in a physician's office rather than in a substance abuse treatment program or clinic where other ancillary services are available? 	<p>Slide 102</p>
<p>QUESTIONS?</p>	<p>Slide 103: Questions?</p> <p><i>Ask if anyone has any questions.</i></p>	<p>Slide 103</p> 

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