blending initiative
NIDA • SAMHSA

Prescription Opioid Addiction Treatment Study (POATS)

Findings and Strategies from a NIDA Clinical Trials Network Study

Training Manual

Prescription Opioid Addiction Treatment Study

Findings and Strategies from a NIDA Clinical Trials Network Study

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Prescription Opioid Addiction Treatment Study

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) has 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 researchers work with representatives from the ATTC network to provide the results and strategies for implementing these findings into clinical settings. This will decrease the time it takes for research to be incorporated into treatment settings and will thereby to 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. Since that time, the CTN completed several clinical trials related to specific uses of this medication. One of these trials looked at strategies for medically-assisted withdrawal from opioids using buprenorphine with prescription opioid dependent adults. This training presents the relevant background for the study as well as the procedures and results. The training ends by examining the implications of the results of the study and how these results might shape the way that services are provided in real-world clinical settings.

Blending Team Members

- Thomas Freese, PhD – Co-Chair – Pacific Southwest ATTC
- Beth Rutkowski, MPH – Co-Chair – Pacific Southwest ATTC
- Leslie Cohen – ATTC of New England
- Joshua D. Lee, MD, MSc – New York University, Longone Medical Center
- Traci Rieckmann, PhD – Northwest Frontier ATTC
- Jennifer Sharpe Potter, PhD, MPH – University of Texas
- Hilary Smith Connery, MD, PhD – Harvard Medical School, McLean Hospital
- Roger Weiss, MD – Harvard Medical School, McLean Hospital

What Does the Training Package Contain?

- PowerPoint Training Slides
- Training Manual with detailed instructions for how to convey the information and conduct the interactive exercises
- Buprenorphine Fact Sheet for Clinicians
- Methadone Fact Sheet for Clinicians
- Naltrexone Fact Sheet for Clinicians
- POATS Resource List

What Does This Training Manual Contain?

The objectives of this Module are to:

1) Define the prevalence and treatment admission rates of prescription opioid dependence in the United States;
2) Describe the mechanism of action of buprenorphine-naloxone;
3) Review the results of a clinical trial that examined the use of buprenorphine-naloxone to treat prescription opioid dependent adults; and
4) Describe the implications of these findings for the treatment of prescription opioid dependence.

This Module can be used as a stand-alone training of approximately 3 hours in length, or can be added to the larger Buprenorphine Awareness training to focus additional attention on treatment of prescription opioid dependent adults.

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 adapted at the discretion of the trainer(s).

How Are the PowerPoint Training Slides Organized?

For this manual, text that is shown in bold italics is a "***Note to the Trainer.***" Text that is shown in normal font relates to the "Trainer's Script" for the slide.

It is important to note that many slides in this training contain some animation. Animations are used to call attention to particular aspects of the information or to present the information in a stepwise fashion to facilitate both the presentation of information and participant understanding. Because of this, some information is hidden when slides first appear on the screen and then comes in as the slide is advanced. No special notes are made if the animation simply causes the next row of text to appear. However, when the animations are complex, step-by-step instructions are provided.

General Information about Conducting the Training

The training is designed to be conducted in small- to medium-sized groups (10-25 people). It is possible to use these materials with larger groups, but the trainer will have to adapt the small group exercises to ensure that there is adequate time to cover all of the material.

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

- Prepared materials for two Interactive Activities – Number Line Activity (slide 43) and Gallery Walk (slides 119-121)

Overall Training Notes

It is critical that, prior to conducting an actual training, the trainer practice using this guide while showing the slide presentation in Slideshow Mode in order to be prepared to use the slides in the most effective manner.

 Note to trainer

 Activity

 References

Buprenorphine Suite: 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
- Prescription Opioid Addiction Treatment Study: Findings and Strategies from a NIDA Clinical Trails 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 wish to incorporate elements of two or more 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.

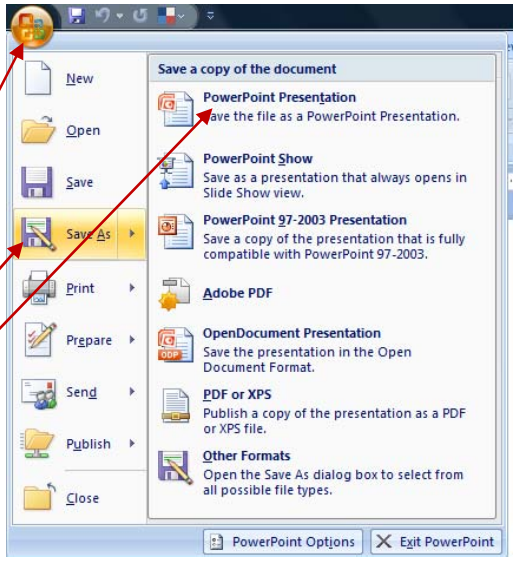
PowerPoint 2007

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.

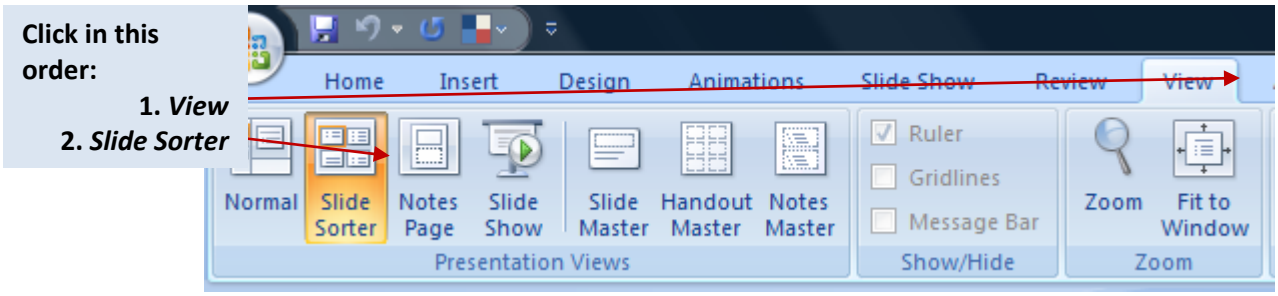
Click in this order:
1. *Program Icon*
2. *Save As*
3. *PowerPoint Presentation*



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

III. Select Slide Sorter view.

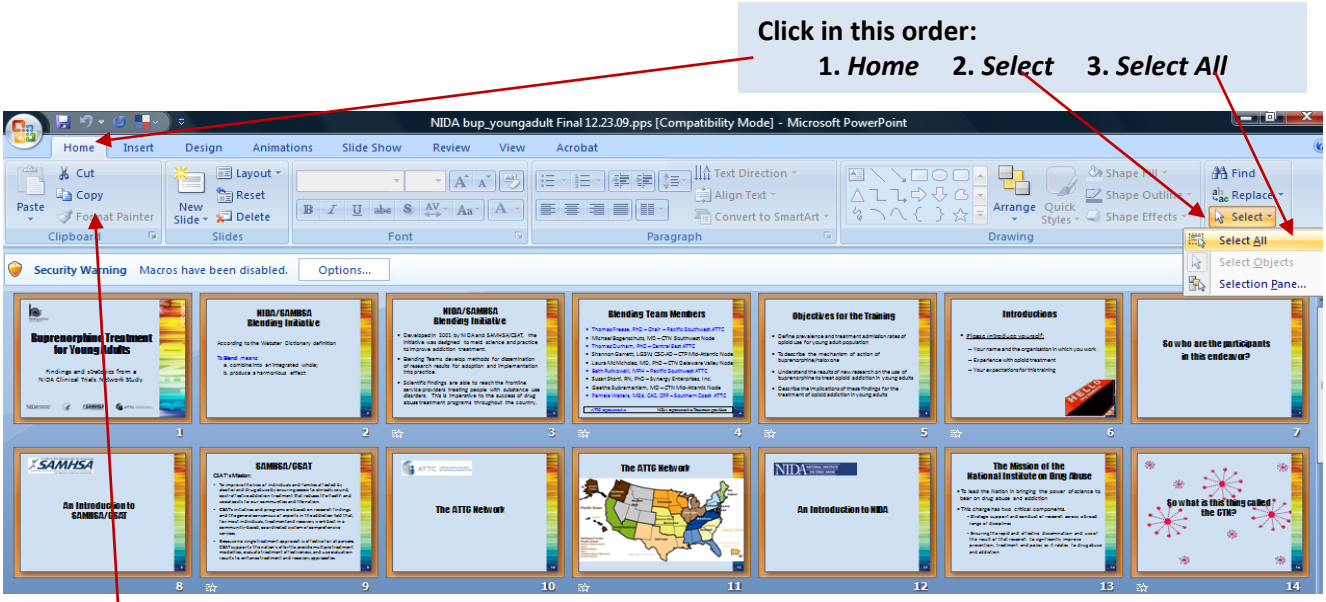
Go to the Slide Sorter view by (1) clicking on ***View*** from the menu at the top of the page and then (2) clicking ***Slide Sorter*** located on the left side of the page near the top.



IV. Select the slides to be copied.

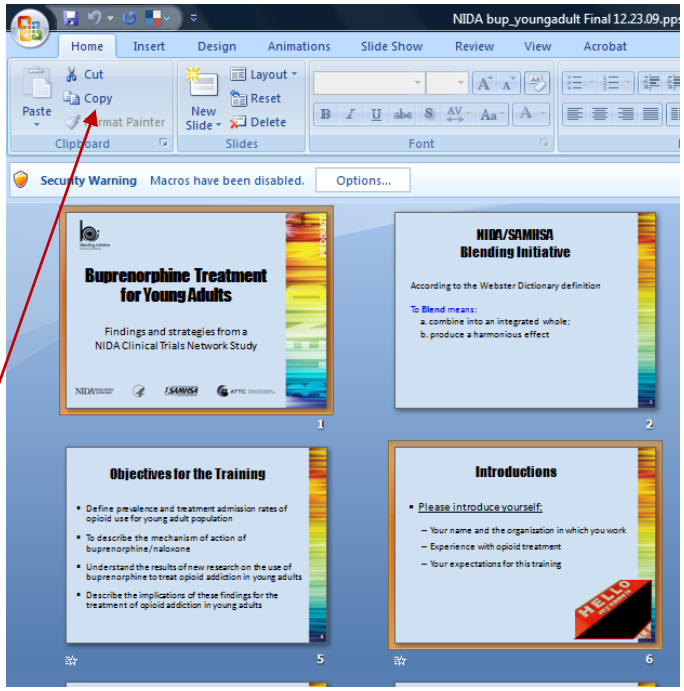
Slides can be copied in two ways. You can select all slides in the presentation, or you can choose only certain slides to copy. Instructions for each are presented below

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.



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

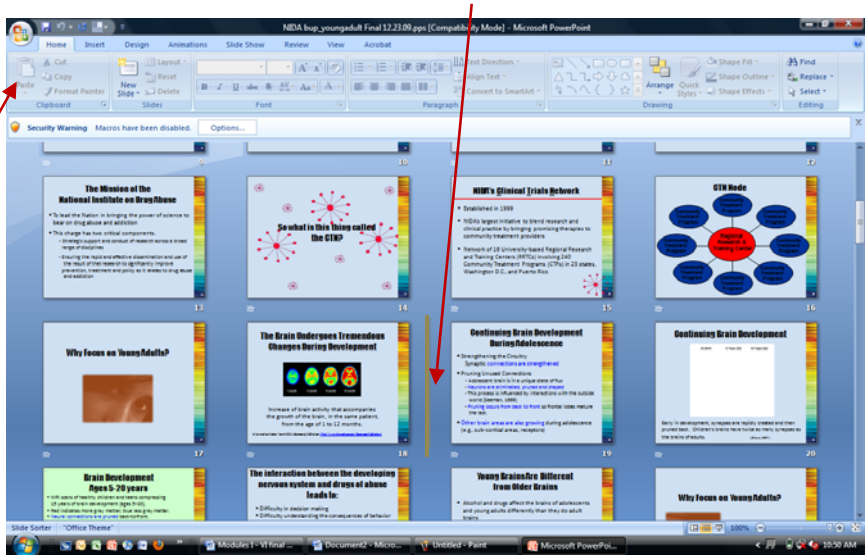
Select specific slides to copy. To copy only certain slides (rather than all of them), on your computer keyboard, hold down the control (***Ctrl***) button. While holding down ***Ctrl***, click on the slides that you want to copy into the combined presentation. Only slides on which you click will be 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.

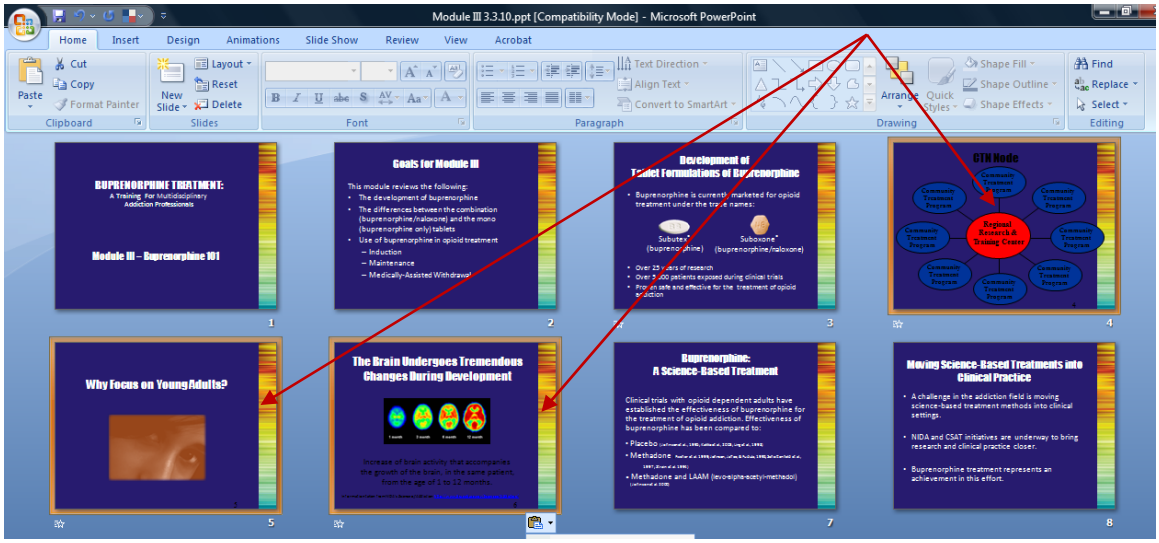
V. Paste the copied slides into your presentation.

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.

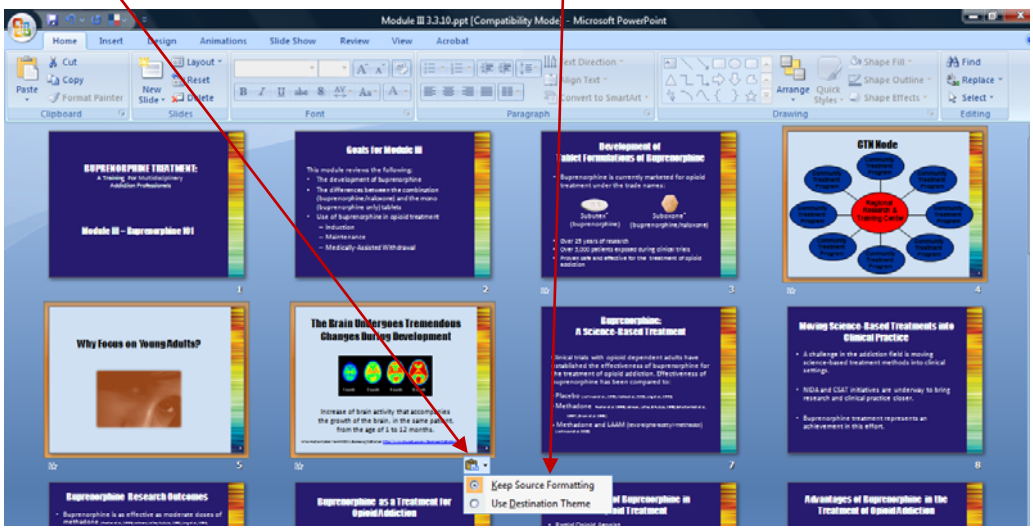
When copying slides from one presentation to the other, the formatting of the copied slides will be altered to match the presentation into which they are inserted. However, this often leads to significant formatting irregularities. In the example below, Slides 4 to 6 were inserted using the method described 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.



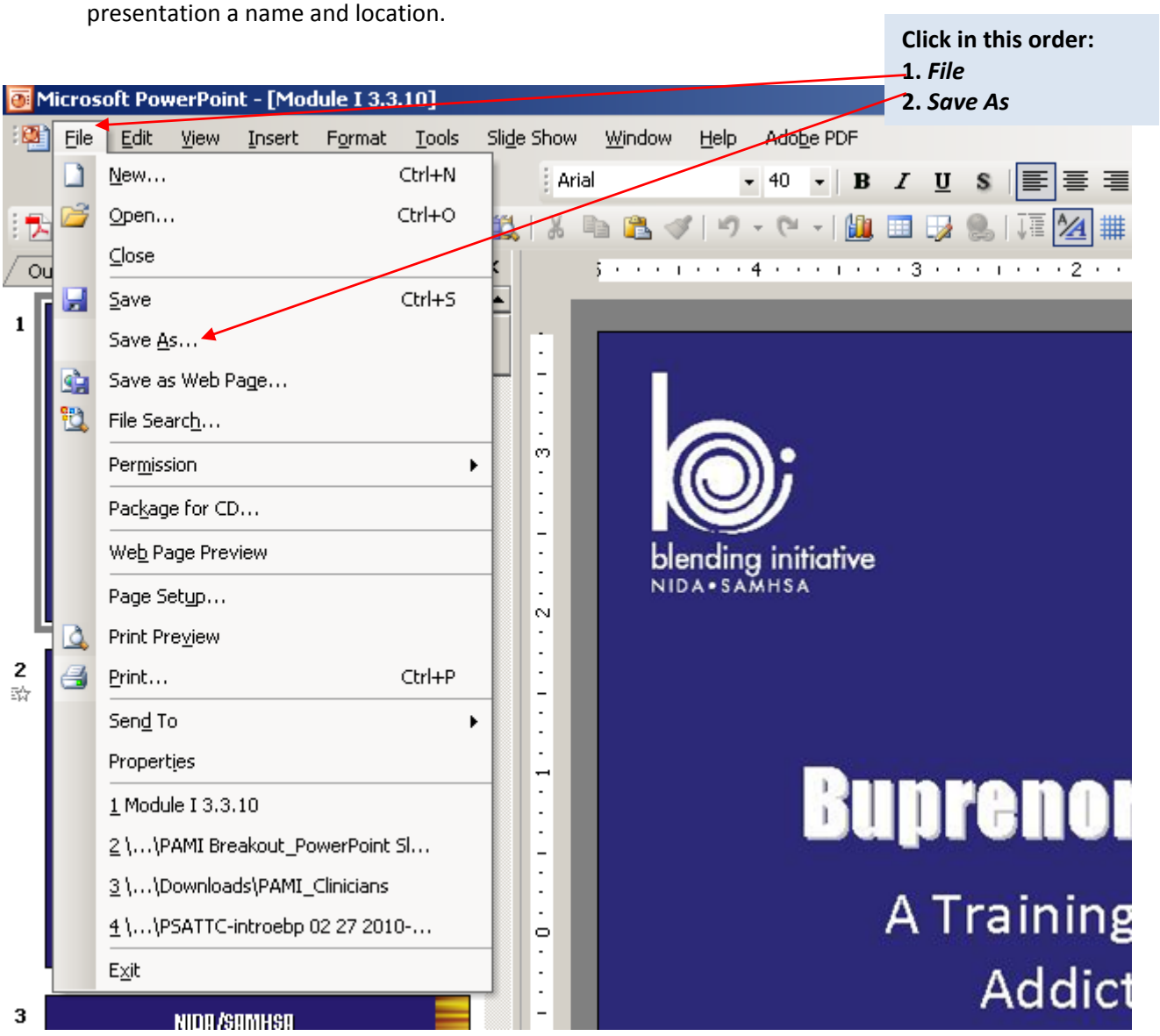
This will restore the formatting from the original presentation and ensure that the slides are legible when projected during a training session.

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.

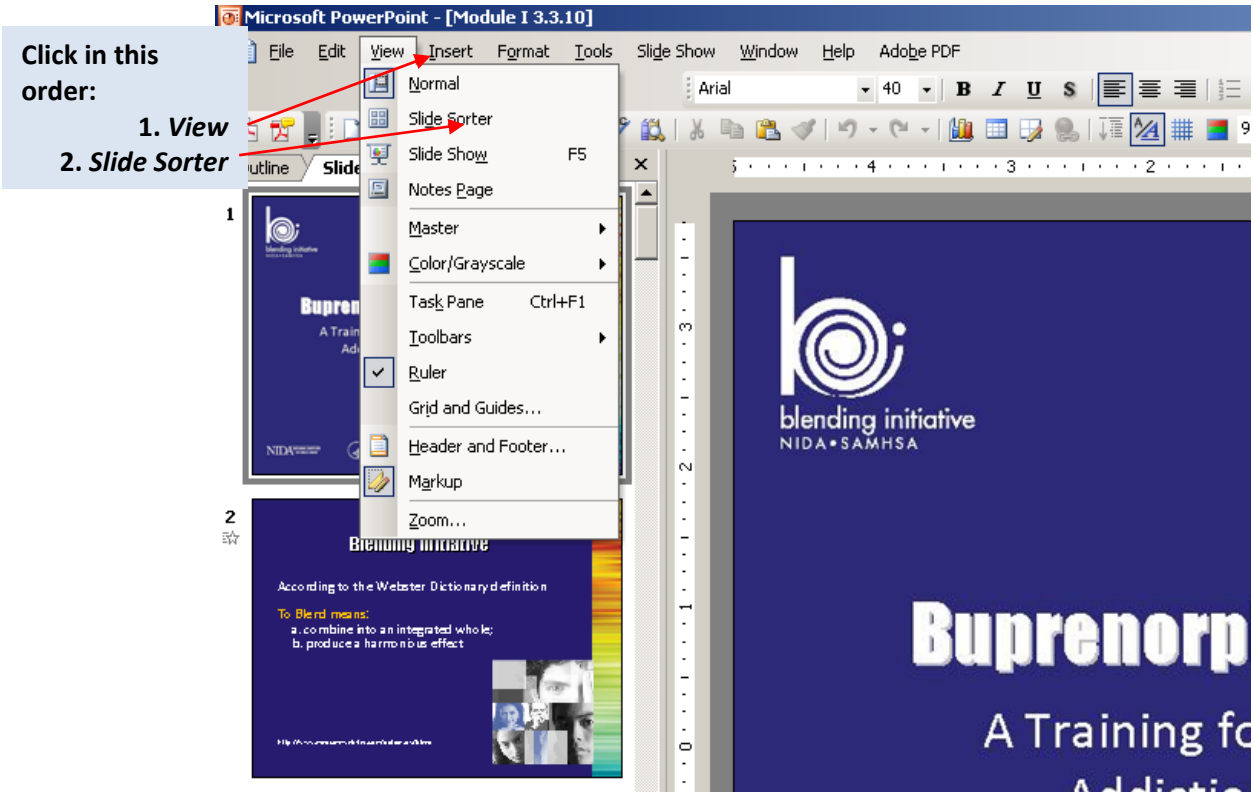
(1) Click on the ***File*** button in the upper left corner of the toolbar and then (2) click on ***Save As*** from the drop-down menu. A dialogue box will appear that will allow you to give the presentation a name and location.



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

III. Select Slide Sorter view.

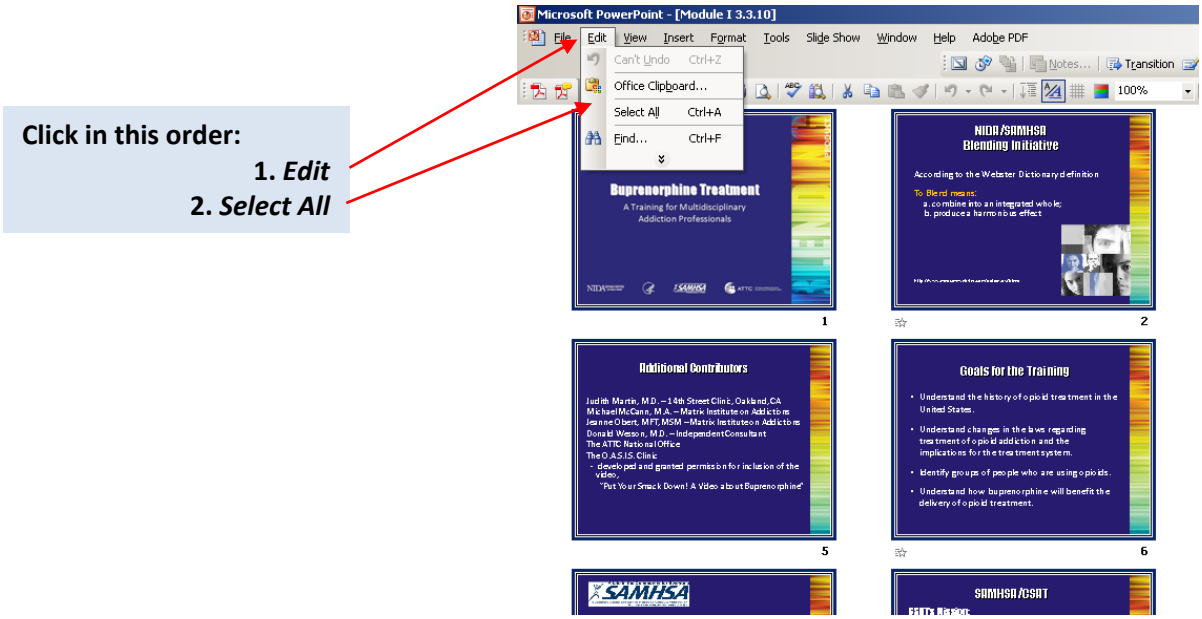
Go to the Slide Sorter view by (1) clicking on ***View*** from the menu at the top of the page and then (2) clicking ***Slide Sorter*** from the drop-down menu.



IV. Select the slides to be copied.

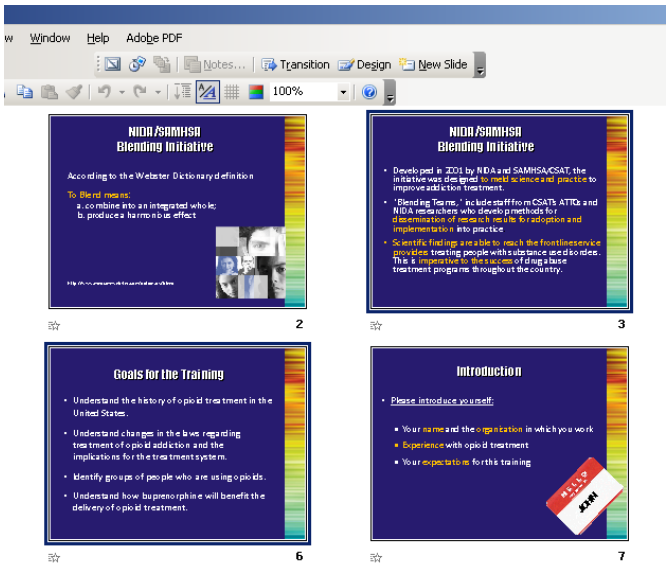
Slides can be copied in two ways. You can select all slides in the presentation, or you can choose only certain slides to copy. Instructions for each are presented below.

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.

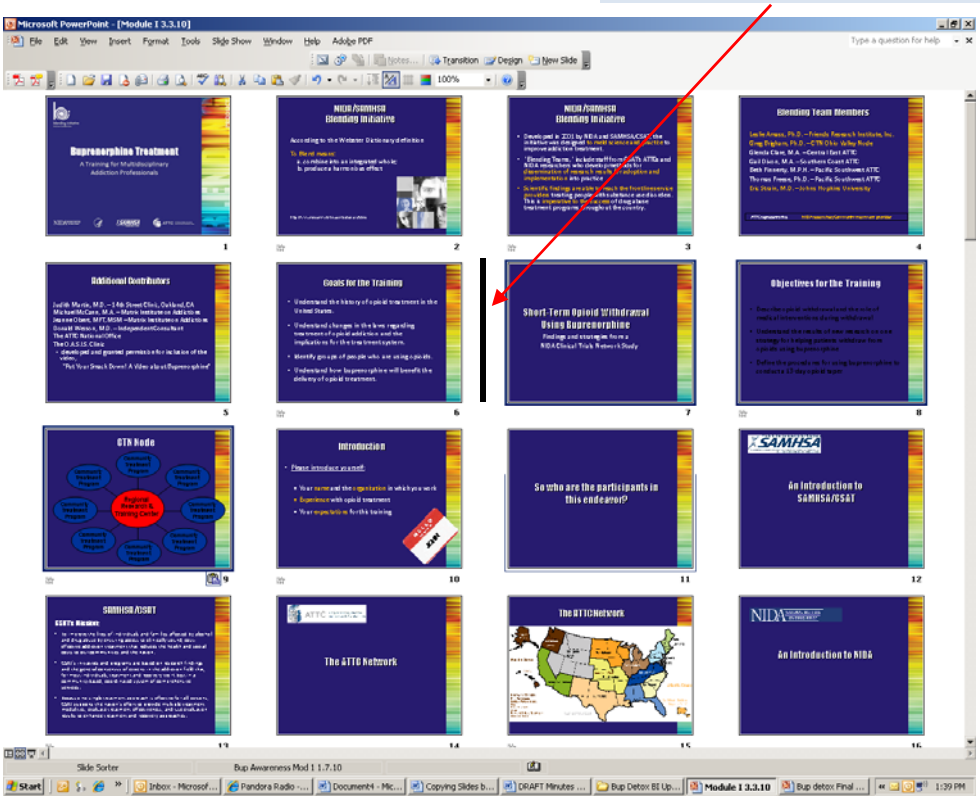


Note: You may want to practice copying a few slides at a time until you are comfortable with this procedure.

V. Paste the copied slides into your presentation.

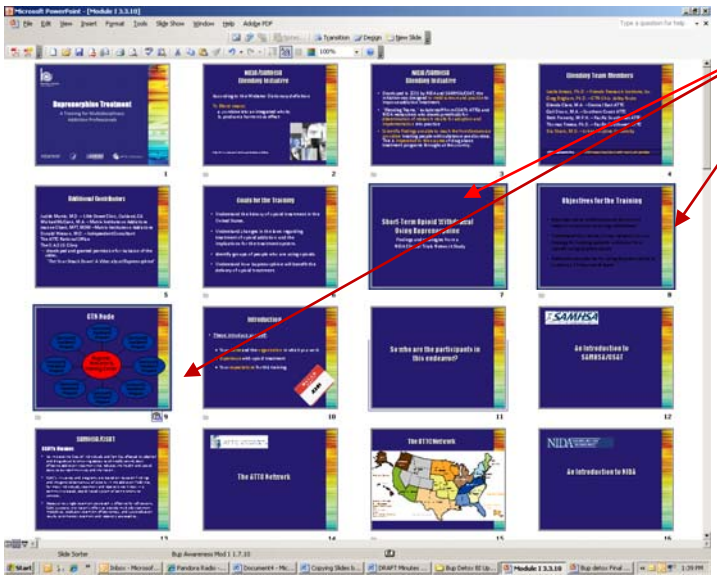
Open your master presentation (the presentation into which the slides are to be copied). Again go to the ***Slide Sorter View*** as described in Step III above. (1) Click in the space between the slides where you would like the copied slides to appear. A flashing line will appear between the slides.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



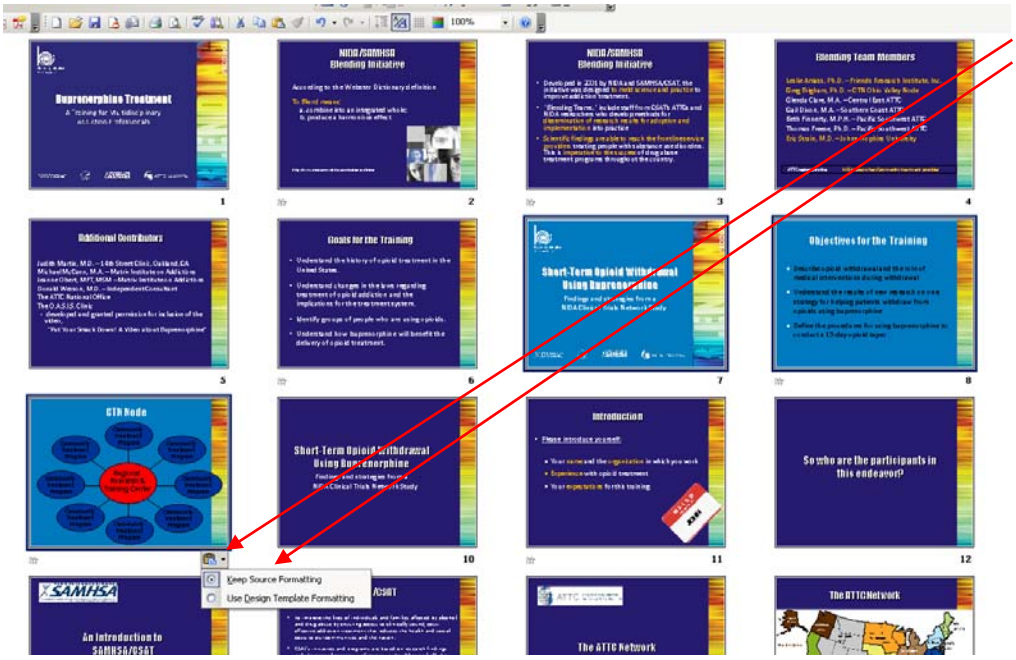
VI. Maintain original formatting.

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.

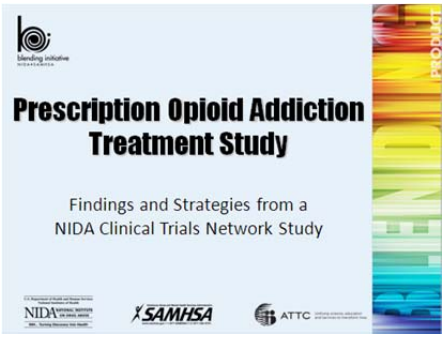
After pasting the slides into the presentation, you will notice that a small clipboard appears near the last inserted slide.



(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.

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).



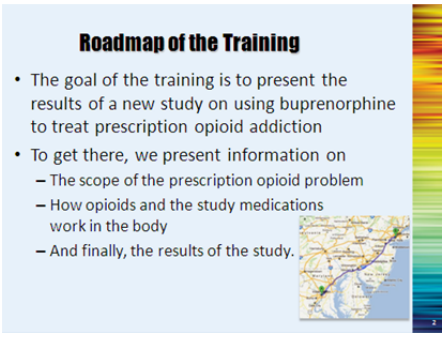
Slide 1: Title Slide

Welcome participants and take care of housekeeping announcements, such as location of restrooms, turning off cell phones, participating actively, etc.

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.

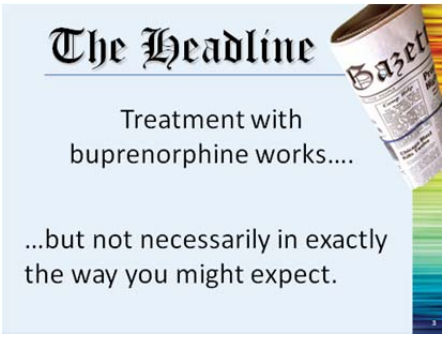
It is important to note that this training is introductory and is focused on building awareness and encouraging multidisciplinary addiction professionals to learn more about buprenorphine and its role in opioid addiction treatment. It is NOT designed to provide an expert level of competency in utilizing buprenorphine for the treatment of opioid addiction.

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 substance use disorders treatment setting.



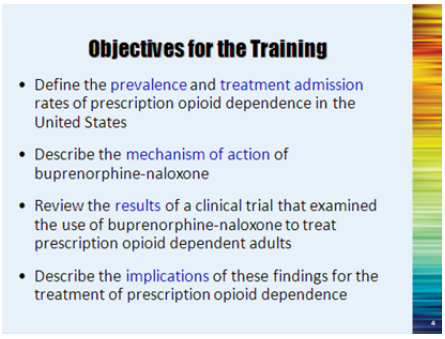
Slide 2: Roadmap of the Training

This slide provides participants with a "road map" of the training presentation. The main goal of the training is to introduce key findings from a new clinical trial on the use of buprenorphine to treat prescription opioid addiction, but before those results are presented, participants will learn more about the epidemiology of the prescription opioid problem and how opioids and the study medication, specifically, work in the user's body.



Slide 3: The Headline

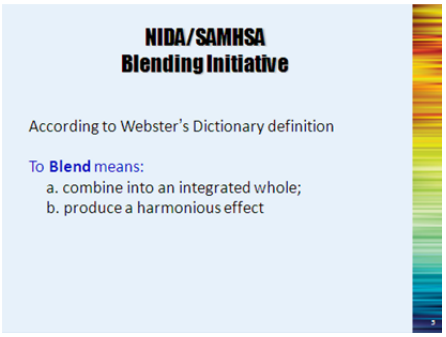
Long-term buprenorphine-naloxone treatment reduces opioid use by those dependent on prescription opioids, according to the first randomized, controlled trial using a medication for the treatment of prescription opioid dependence.



Slide 4: Objectives for the Training

There are four primary objectives for this training:

- To define the prevalence of and treatment admission rates of prescription opioid dependence in the United States;
- To describe the mechanism of action of buprenorphine-naloxone;
- To review the results of a clinical trial that examined the use of buprenorphine-naloxone to treat prescription opioid dependent adults; and
- To describe the implications of these findings for the treatment of prescription opioid dependence.



Slide 5: NIDA/SAMHSA Blending Initiative

Share the definition of "blend" based upon the Merriam-Webster dictionary.

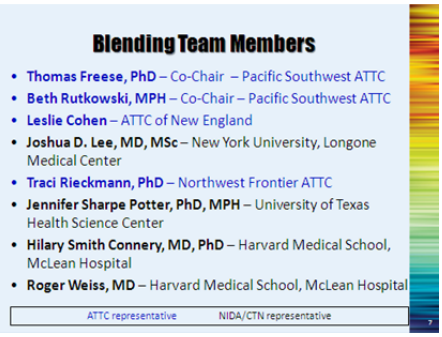
Reference:

blend. (2010). In *Merriam-Webster Online Dictionary*. Retrieved March 16, 2010, from http://www.merriam-webster.com/dictionary/blend

Slide 6: NIDA/SAMHSA Blending Initiative

Initiated 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, 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 disseminate research findings that will accelerate the dissemination of research-based findings into practice.

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 substance use disorders treatment programs throughout the country.



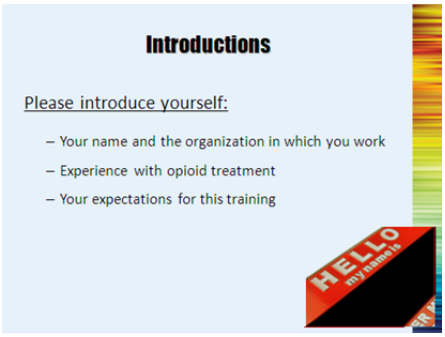
Slide 7: Blending Team Members

Blending Teams are composed of NIDA-funded researchers, community-based substance abuse treatment practitioners, and trainers and technology transfer specialists from SAMHSA's Addiction Technology Transfer Center (ATTC) Network who work closely together to develop the NIDA/SAMHSA Blending Products.

Acknowledge the members of the Blending Team who created this module. Note that the membership consisted of four ATTC representatives and four NIDA/CTN representatives.

Slide 8: Special Acknowledgements

Acknowledge the additional individuals who contributed to the development of the POATS Blending Product.



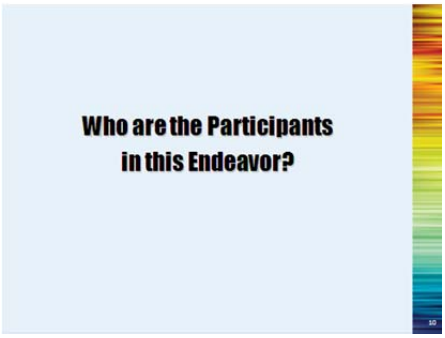
Slide 9: Introductions

<u>For smaller groups (20 or less):</u> 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 addition treatment, and what they expect to gain from the training.

<u>For larger groups:</u> 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.

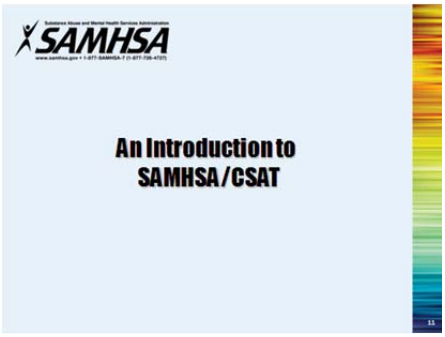
At a minimum, ask:
Who is:

- ***A direct treatment provider***
- ***A counselor***
- ***A nurse***
- ***A physician***
- ***A social worker***
- ***An administrator***
- ***An educator***
- ***Is there anyone I missed?***



Slide 10: Who are the Participants in this Endeavor?
(Transition Slide)

So now we will introduce the key participants who helped to develop these training materials.



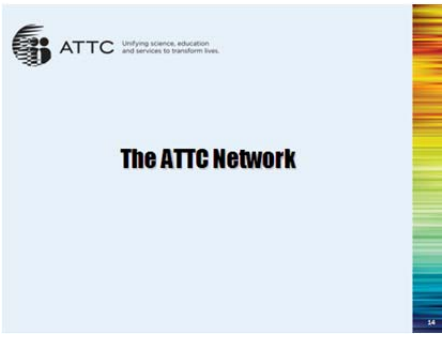
Slide 11: An Introduction to SAMHSA/CSAT
(Transition Slide)

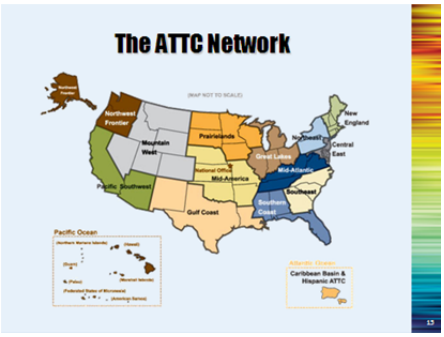
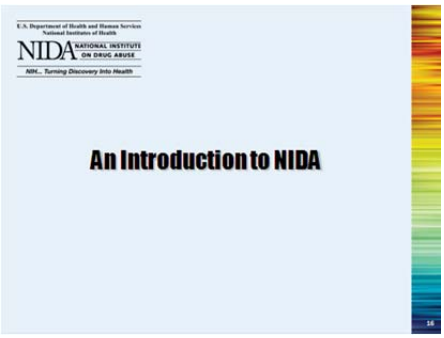
The Center for Substance Abuse Treatment (CSAT) of the Substance Abuse and Mental Health Services Administration (SAMHSA), U.S. Department of Health and Human Services (DHHS), was created in October 1992 with a congressional mandate to expand the availability of effective treatment and recovery services for alcohol and drug problems.

Slide 12: Substance Abuse and Mental Health Services Administration

Behavioral health services improve health status and reduce health care and other costs to society. SAMHSA is charged with effectively targeting substance abuse and mental health services to the people most in need and to translate research in these areas more effectively and more rapidly into the general health care system. Continued improvement in the delivery and financing of prevention, treatment, and recovery support services provides a cost-effective opportunity to advance and protect the Nation's health.

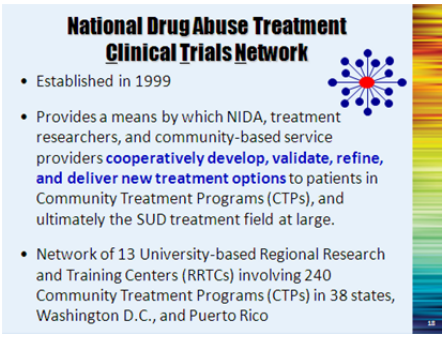
Additional Information for the Trainer(s):
SAMHSA has identified eight Strategic Initiatives to focus its resources on areas of urgency and opportunity. They also will enable SAMHSA to respond to National, State, Territorial, Tribal, and local trends and support implementation of the Affordable Care Act and the Mental Health Parity and Addictions Equity Act. People are at the core of SAMHSA's mission, and these Initiatives will guide its work through 2014 to help people with mental and substance use disorders and their families, build and support strong and supportive communities, prevent costly and painful behavioral health problems, and promote better health and functioning for all Americans.

	**Slide 13: SAMHSA's Center for Substance Abuse Treatment**  ***Read CSAT mission.*** ***Highlight the importance of the research base in all of CSAT's programming and educating the field about the advances of science to continually improve the quality of services provided.***
	**Slide 14: The ATTC Network** ***(Transition Slide)*** One of the major vehicles that SAMHSA has for ensuring that the workforce is adequately trained is the Addiction Technology Transfer Center (ATTC) Network.

	**Slide 15: The ATTC Network** Fourteen regional Centers and a National Office comprise the ATTC Network, which is dedicated to identifying and advancing opportunities for improving addiction treatment. The vision of the ATTC Network is to unify science, education and services to transform the lives of individuals and families affected by substance use disorders. The ATTC Network trains the substance use disorders treatment and recovery workforce on evidence-based practices. 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. The ATTC Network is committed to helping the substance use disorders treatment and recovery services field stay abreast of what works in order to enhance their skills and change their practice.
	**Slide 16: An Introduction to NIDA** ***(Transition Slide)*** The National Institute on Drug Abuse (NIDA) was established in 1974, and in October 1992, it became part of the National Institutes of Health, Department of Health and Human Services. Recent scientific advances have revolutionized our understanding of drug abuse and addiction. The majority of these advances, which have dramatic implications for how to best prevent and treat addiction, have been supported by NIDA.

Slide 17: The Mission of the National Institute on Drug Abuse

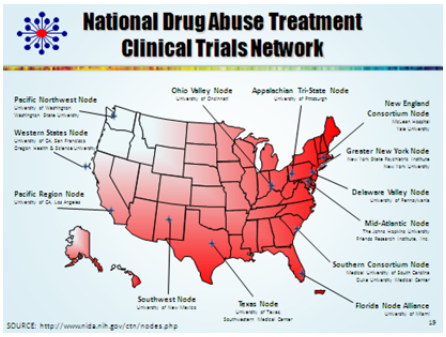
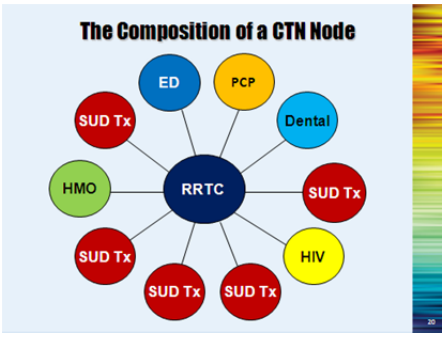
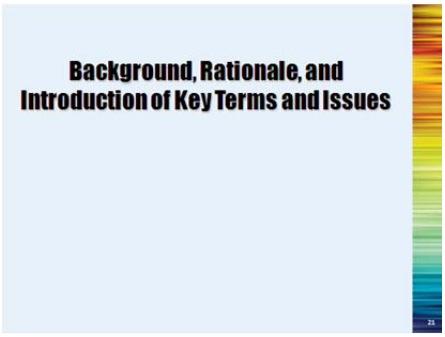
NIDA is not only seizing upon unprecedented opportunities and technologies to further the understanding of how drugs of abuse affect the brain and behavior, but also working to ensure the rapid and effective transfer of scientific data to policy makers, drug abuse practitioners, other health care practitioners, and the general public. The scientific knowledge that is generated through NIDA-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.

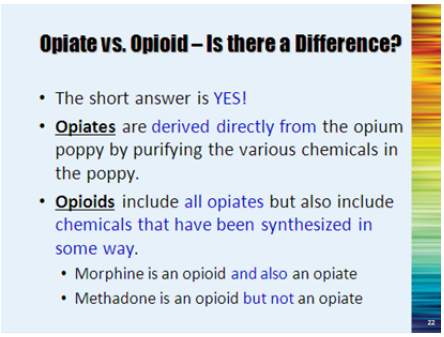


Slide 18: National Drug Abuse Treatment Clinical Trials Network

The mission of the CTN is two-fold:

- To 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
- To transfer the research results to physicians, providers, and their patients to improve the quality of substance use disorders treatment throughout the country using science as the vehicle.

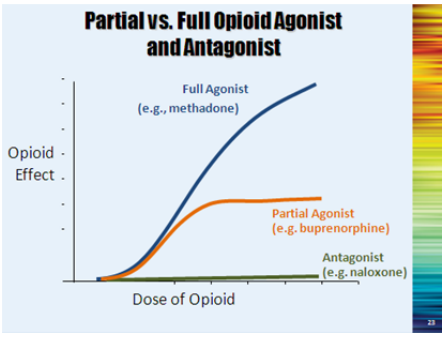
	**Slide 19: National Drug Abuse Treatment Clinical Trials Network** This map shows the geographic distribution of the 13 University-Based Regional Research and Training Centers (RRTCs) that work with 240 Community Treatment Programs (CTPs) in 38 states, Washington, D.C., and Puerto Rico.
	**Slide 20: The Composition of a CTN Node** Although initially RRTCs only worked with community treatment programs (CTPs), the CTN now encompasses more than just CTPs; RRTCs also partner with primary care and community health centers, hospitals, HIV clinics, emergency rooms, university medical centers, HMOs, to implement CTN research protocols on a variety of cutting edge topics.
	**Slide 21: Background, Rationale, and Introduction of Key Terms and Issues** ***(Transition Slide)*** The abuse of prescription opioids is a significant public health and policy concern, given increasing rates of non-medical use, emergency department visits, addiction treatment episodes, overdose deaths, and costs related to these drugs in recent years. This portion of the presentation will provide background information and will introduce key terms and issues that will be woven throughout the presentation.



Slide 22: Opiate vs. Opioid – Is there a Difference?

The term "opiate" refers only to drugs or medications that are derived directly from the opium poppy. Examples include heroin, morphine, and codeine.

The term "opioid" is a broader term referring to opiates and other synthetically-derived drugs or medications that operate on the opioid receptor system and produce effects similar to morphine. Examples include buprenorphine and methadone.



Slide 23: 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.

NOTES FOR SLIDE 23 CONTINUED FROM PREVIOUS PAGE	**Slide 23: Partial vs. Full Opioid Agonist and Antagonist**  ***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 24: The Prescription Drug Epidemic is Unique in Some Ways

Unlike illicit drugs like heroin, cocaine, and methamphetamine, prescription medications are not illegal or inherently harmful. There has been an increase in legitimate commercial production and distribution of pharmaceuticals, as well as an increase in marketing to physicians and public regarding the availability of opioid pain medications. Some physicians have become more willing to prescribe medications, especially for pain management.

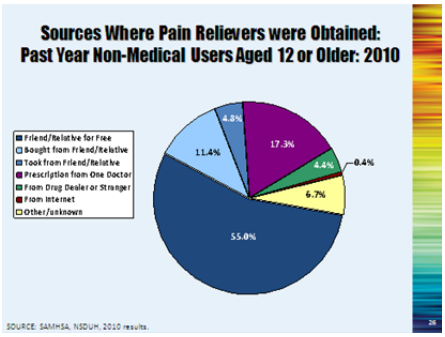
Additional Information for the Trainer(s):
In the terminology of the United States Drug Enforcement Administration (DEA), **diversion** is the use of prescription drugs for recreational purposes. The term comes from the "diverting" of the drugs from their original purposes. The DEA employs Diversion Investigators to address these problems.

Slide 25: Prescription Drugs are Easy to Obtain

Review the list of possible sources of prescription medications.

Ask participants to provide examples of other places people might access prescription medications.

Additional Information for the Trainer(s):
It seems likely that young people are less concerned about the dangers of using these drugs outside of medical regimen, likely because they are widely used for legitimate purposes. Also, prescription medications are now being advertised directly to the consumer, which implies both that they are used widely and are safe to use.

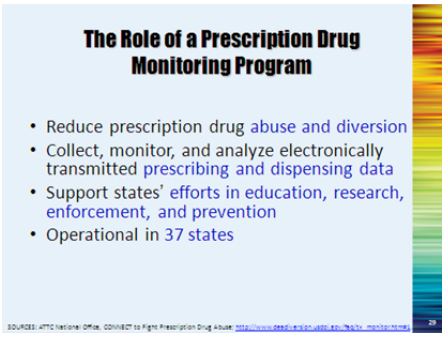
	**Slide 26: Sources Where Pain Relievers were Obtained: Past Year Non-Medical Users Aged 12 or Older: 2010** The majority of individuals who use prescription drugs non-medically, for unintended purposes, obtain the drugs from friends or family members.
	**Slide 27: Safe Disposal of Prescription Drugs, Part 1** Do not flush prescription drugs down the toilet or drain unless the label or accompanying patient information specifically instructs you to do so. To dispose of prescription drugs not labeled to be flushed, you may be able to take advantage of community drug take-back programs or other programs, such as household hazardous waste collection events, which collect drugs at a central location for proper disposal. Call your city or county government's household trash and recycling service and ask if a drug take-back program is available in your community.

Slide 28: Safe Disposal of Prescription Drugs, Part 2

The National Take Back initiative scheduled by DEA to provide a venue for persons who want to dispose of unwanted and unused prescription drugs (http://www.deadiversion.usdoj/gov/drug_disposal/takeback/index.html)

If a drug take-back or collection program is not available, there are several steps you can take to safely dispose of unused prescription drugs.

Be sure to conceal or remove any personal information, including prescription (Rx) number, on the empty containers by covering it with black permanent marker or duct tape, or by scratching it off.

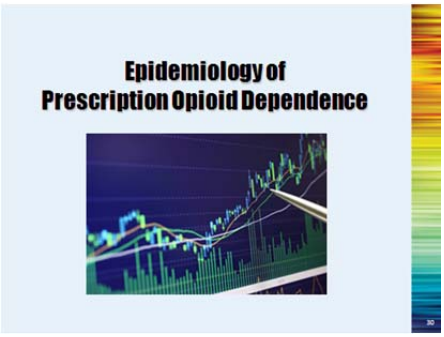


Slide 29: The Role of a Prescription Drug Monitoring Program

The PMP Center of Excellence seeks to end the prescription drug abuse epidemic in the United States without compromising accepted standards of pain management or the legitimate prescribing of controlled substances. PDMPs are a tool that states can use to address prescription drug abuse, addiction and diversion, and may serve several purposes, such as to: (1) support access to legitimate medical use of controlled substances; (2) identify and deter or prevent drug abuse and diversion; (3) facilitate and encourage the identification, intervention with, and treatment of persons addicted to prescription drugs; (4) inform public health initiatives through outlining of use and abuse trends; and (5) educate individuals about PDMPs and the use, abuse, and diversion of and addiction to prescription drugs.

As of December 2011, 48 states and 1 U.S. territory had legislation authorizing the creation and operation of a PDMP. Thirty-seven states have operational PDMPs that have the capacity to receive and distribute controlled substance prescription information to authorized users. Additional information is available at http://www.pmpalliance.org, including a PDMP program status map.

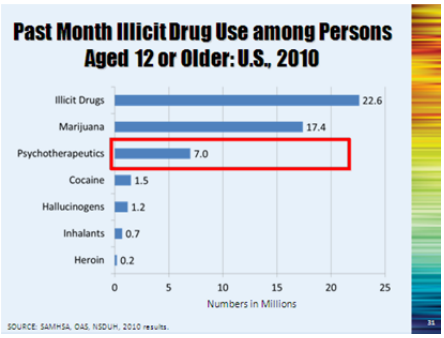
The PMP Information Exchange (PMIX) program enables the interstate exchange of PDMP data.



Slide 30: Epidemiology of Prescription Opioid Dependence
(Transition Slide)

The next series of slides focus specifically on the prevalence of prescription opioid abuse in the United States.

IMAGE COURTESY OF SAMHSA WEBSITE (www.samhsa.gov; data page)



Slide 31: Past Month Illicit Drug Use among Persons Aged 12 or Older: U.S., 2010

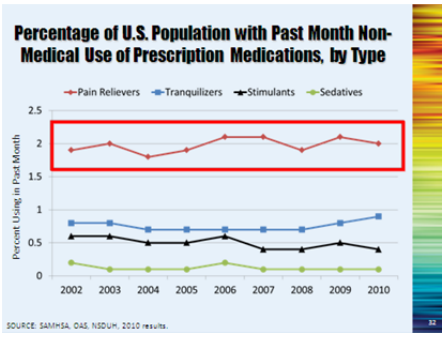
In 2010, 22.6 million individuals aged 12 or older reported past month use of any illicit drug.

Prescription medications (psychotherapeutics) were the second most prevalent drug, following marijuana. Approximately 7 million individuals used a prescription medication non-medically at least once in the past month.

The use of a prescription opioid for non-medical reasons was 20 times more common than was heroin use.

Almost 50% more people sought treatment for dependence on prescription opioids than for dependence on heroin.

Alcohol is not included on this graph. As a point of reference, in 2010, there were a reported 131.3 million past month alcohol users in the U.S.



Slide 32: Percentage of U.S. Population with Past Month Non-Medical Use of Prescription Medications, by Type

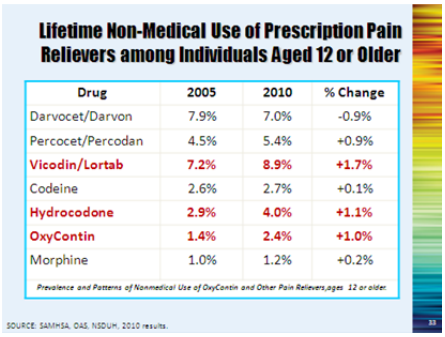
National Survey on Drug Use and Health (NSDUH) respondents are asked to report only "non-medical" use of prescription medications, defined as use without a prescription of the individual's own or simply for the experience or feeling the drugs caused. Use of over-the-counter drugs and legitimate use of prescription drugs are not included. NSDUH reports combine the four prescription-type drug groups (pain relievers, stimulants, tranquilizers, and sedatives) into a category referred to as “psychotherapeutics.”

The number and percentage of current non-medical users of psychotherapeutic drugs in 2010 (7.0 million or 2.8%) were higher than in 2008 (6.2 million or 2.5%).

Pain relievers are the most prevalent class of pharmaceuticals used by survey respondents, and are driving the drastic increases seen nationwide in prescription medication abuse.

Though higher than in 2008, the 2010 rates for any psychotherapeutic drug use were similar to those in 2009.

Additional Information for the Trainer(s):
Research indicates that 5 to 23 percent of all prescription opioid doses dispensed are used non-medically (Katz et al., 2010). This expanded access to controlled substances has been linked to a greater number of negative health outcomes and increased health care costs.



Slide 33: Lifetime Non-Medical Use of Pain Relievers among Individuals Aged 12 or Older

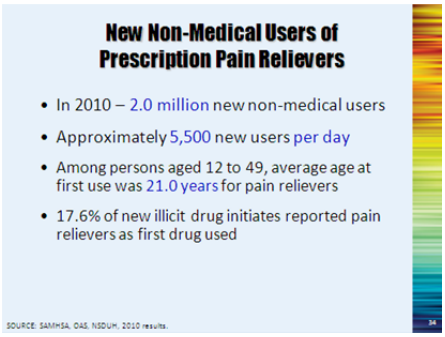
In 2010, Vicodin/Lortab, Darvocet/Darvon, and Percocet/Percodan were the most frequently reported prescription pain relievers among all respondents.

The rates of lifetime non-medical use of certain pain relievers (Vicodin, hydrocodone, and OxyContin) are even more alarming when you compare the 2010 rates with those from 2005.

The largest increases were seen for Vicodin/Lortab, hydrocodone, and OxyContin.

Percentages were highest among individuals aged 18 to 25 (data not shown).

The red text that appears in the table is used to denote the greatest percentage point increases among specific pain relievers between 2005 and 2010. These increases, however, are not necessarily statistically significant.



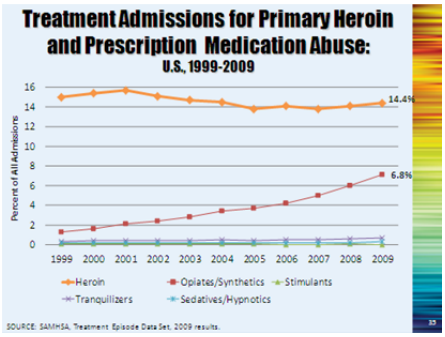
Slide 34: New Non-Medical Users of Prescription Pain Relievers

Information on substance use initiation, also known as incidence or first-time use, is important for policymakers and researchers. Measures of initiation are often leading indicators of emerging patterns of substance use. They provide valuable information that can be used to assess the effectiveness of current prevention programs and to focus prevention efforts. NSDUH provides a variety of estimates related to initiation of substance use (illicit drugs, cigarettes, and alcohol) based on reported age and on year and month at first use. Individuals who initiated use within the past 12 months are referred to as recent or past year initiates.

Data from the 2010 NSDUH show that 2.0 million people aged 12 or older, initiated non-medical use of prescription pain relievers within the past year. This averages to approximately 5,500 initiates (new users) per day.

New users of prescription pain relievers were slightly older than new users of inhalants (16.3 years), marijuana (18.4 years), or Ecstasy (19.4 years), but were younger than new users of cocaine (21.2 years), heroin (21.3 years), or prescription tranquilizers (24.6 years).

Additional Information for the Trainer(s):
In 2010, of the 3.0 million persons aged 12 or older who used illicit drugs for the first time within the past 12 months, a majority reported that their first drug was marijuana (61.8%). About one quarter initiated with psychotherapeutics (26.2%, including 17.3% with pain relievers, 4.6% with tranquilizers, 2.5% with stimulants, and 1.9% with sedatives). A notable proportion reported inhalants (9.0%) as their first drug, and a small proportion used hallucinogens as their first illicit drug (3.0%). All of the above percentages of first drug use were similar to the corresponding percentages in 2009.



Slide 35: Treatment Admissions for Primary Heroin and Prescription Medication Abuse: U.S., 1999-2009

The proportion of all substance abuse treatment admissions aged 12 or older that reported primary other opiate abuse increased seven-fold between 1999 and 2009, from 1% to 6.8%.

Increases in percentages of admissions reporting non-heroin opiate abuse cut across age, gender, race/ethnicity, education, employment, and region.

Additional information for the Trainer(s):
Just over half (54%) of primary non-heroin opiate admissions were male.

Most primary non-heroin opiate admissions (88%) were non-Hispanic White.

48% of admissions for non-heroin opiates were aged 20 to 29 compared to 30% of all admissions. The peak age at admission for both males and females was about 25 years.

About one in five (19%) non-heroin opiate abusers had a treatment plan that included medication-assisted opioid therapy.

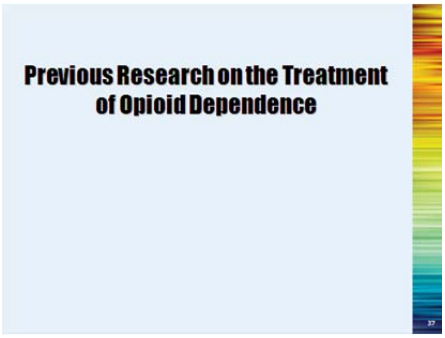
62% of admissions for primary non-heroin opiates reported abuse of other substances. The most commonly reported secondary substances of abuse were marijuana (25%), alcohol (22%), and tranquilizers (12%).

Slide 36: Gender Differences in Prescription Opioid Abuse

Jamison and colleagues recommended that women who are taking opioids to treat non-cancer chronic pain and show signs of "significant affective stress" should receive treatment for the mood disorder and counseling on the dangers of relying on opioids to reduce stress and improve sleep.

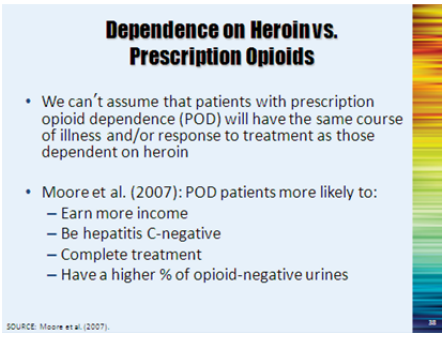
For male patients taking opioids for non-cancer chronic pain, doctors should closely monitor known or suspected behavioral problems, conduct frequent urine screenings, pill counts and compliance monitoring.

The implications of this study are important to consider when completing comprehensive client intakes and treatment plans.



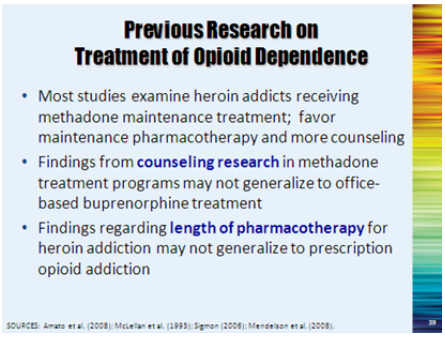
Slide 37: Previous Research on the Treatment of Opioid Dependence
(Transition Slide)

The next series of slides present key research findings regarding the treatment of opioid dependence, including both heroin and other opioids.



Slide 38: Dependence on Heroin vs. Prescription Opioids

The research conducted by Moore and colleagues has suggested that patients dependent on prescription opioids have more favorable prognostic characteristics than do those dependent on heroin, including shorter treatment histories, less injection drug use, fewer family and social problems, and less income from illegal sources. Moore et al.'s secondary analysis found that patients dependent on prescription opioids (n=29) had less opioid use during office-based buprenorphine-naloxone treatment compared with those using heroin (n=124). Perhaps, then, patients dependent on prescription opioids respond to treatment differently than do those dependent on heroin.



Slide 39: Previous Research on Treatment of Opioid Dependence

Studies examining the role of counseling in the treatment of primarily heroin-dependent patients receiving methadone in specialized opioid treatment programs have generally, although not always, supported the role of drug counseling in improving outcomes, particularly abstinence from opioids. Recent reviews of prescription opioid dependence have also called for examination of the optimal length of pharmacotherapy in this population. Studies of heroin-dependent patients have favored maintenance treatment over detoxification; no studies have examined this issue in patients dependent on prescription opioids.

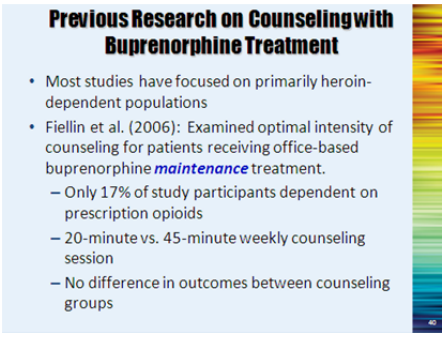
References:

Amato, L., Minozzi, S., Davoli, M., Vecchi, S., Ferri, M.M., & Mayet, S. (2008). Psychosocial combined with agonist maintenance treatments versus agonist maintenance treatments alone for treatment of opioid dependence. *Cochrane Database Syst Rev., 4,* CD004147.

McLellan, A.T., Arndt, I.O., Metzger, D.S., Woody, G.E., & O'Brien, C.P. (1993). The effects of psychosocial services in substance abuse treatment. *JAMA, 269*(15), 1953-59.

Sigmon, S.C. (2006). Characterizing the emerging population of prescription opioid abusers. *Am J Addict, 15*(3), 208-12.

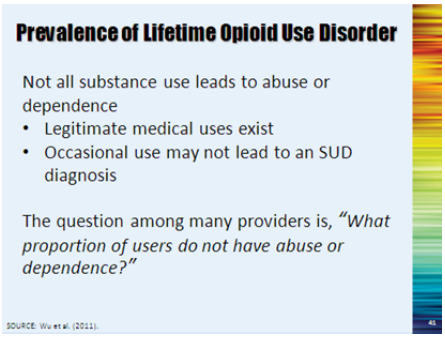
Mendelson, J., Flower, K., Pletcher, M.J., & Galloway, C.P. (2008). Addiction to prescription opioids: Characteristics of the emerging epidemic and treatment with buprenorphine. *Exp Clin Psychopharmacol, 63*(1), 102-09.



Slide 40: Previous Research on Counseling with Buprenorphine Treatment

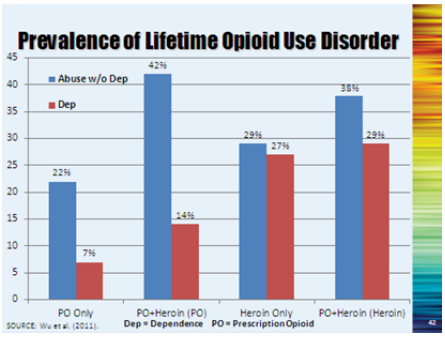
An area in which differential treatment responses could arise is with regards to the role of counseling; the impact of counseling in office-based treatment of individuals dependent on prescription drugs is unknown. The largest study of counseling in conjunction with buprenorphine-naloxone treatment in a primary care office-based setting found no difference between two levels of intensity of counseling, although the difference in intensity between the two counseling conditions (1 weekly session lasting either 20 or 45 minutes) was relatively small, and the sample was primarily (86%) heroin users. Adherence to buprenorphine-naloxone treatment varied; increased adherence was associated with improved treatment outcomes.

Reference:
Fiellin, D.A., Pantalon, M.V., Chawarski, M.C., Moore, B.A., Sullivan, L.E., O'Connor, P.G., & Schottenfield, R.S. (2006). Counseling plus buprenorphine-naloxone maintenance therapy for opioid dependence. *New England Journal of Medicine, 355*, 365-74.



Slide 41: Prevalence of Lifetime Opioid Use Disorder

Not all substance use leads to abuse and dependence. In the case of prescription opioids, there are legitimate medical uses (including treatment of pain, cough, and diarrhea), and occasional use of prescription opioids may not necessary lead to a diagnosis of abuse or dependence.

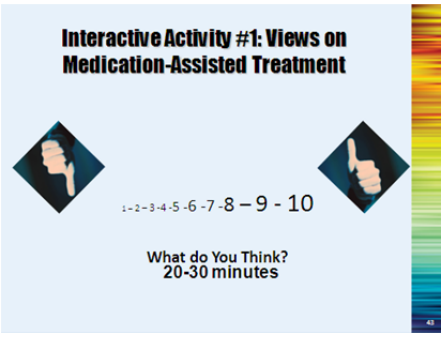


Slide 42: Prevalence of Lifetime Opioid Use Disorder

The take-home message is that heroin use, either alone or in combination with prescription opioid use, is more likely to lead to abuse or dependence than is prescription opioid use.

The second and fourth sets of bars correspond to individuals who use both prescription opioids and heroin. The second set of bars corresponds to the percentage of prescription opioid abuse or dependence specifically among individuals who use both types of opioids. The fourth set of bars corresponds to the prevalence of heroin abuse or dependence specifically among individuals who use both types of opioids. You can see that the rates of heroin abuse or dependence among poly-opioid users are higher than the rates of prescription opioid abuse or dependence.

Reference:
Wu, L-T., Ling, W., Burchett, B., Blazer, D.G., Yang, C., Pan, J-J., Reeve, B.B., & Woody, G.E. (2011). Use of item response theory and latent class analysis to link poly-substance use disorders with addiction severity, HIV risk, and quality of life among opioid-dependent patients in the Clinical Trials Network. *Journal of Drug and Alcohol Dependence, 118*(2-3), 186-93.



Slide 43: Interactive Activity #1: Views on Medication-Assisted Treatment

<u>Option #1 (Preferred): "Virtual Ruler" Version</u>
Preparation prior to the training is needed for this activity. Prepare one sign that says "1 Strongly Disagree" and one that says "10 Strongly Agree." Prior to the training, identify an area where participants can line up, shoulder to shoulder across the room. Post one sign on either side of this area. This will clearly demark the scaling ruler area for this activity.

<u>Option #2: "Jack in the Box" Version</u>
If space does not allow for the method described in Option #1, you may instead ask participants to stand up at their chair, depending on certain responses to the questions posed.

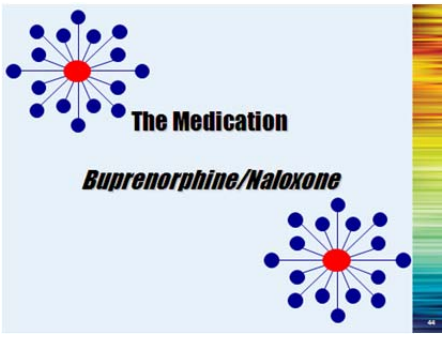
Before we examine the findings of the CTN study, let's talk about your views on the use of medications in the treatment of substance use disorders – also known as pharmacotherapy. Medications are playing an increasingly important role as adjuncts to psychosocial strategies of addiction treatment.

ACTIVITY – 20 to 30 minutes

The purpose of this activity is to increase awareness about practitioner attitudes regarding the use of medications for substance use disorders in adults, and foster open-mindedness to new pharmacotherapies. Option #1 for this activity consists of a "virtual" scaling ruler that spans the training room or other convenient location. The side of the virtual ruler that has a "1" means that the participants "Strongly Disagree" with the statements that are being read.

NOTES FOR SLIDE 43 CONTINUED FROM PREVIOUS PAGE	**Slide 43: Interactive Activity #1: Views on Medication-Assisted Treatment**  The side of the virtual ruler that is marked with a "10" means that participants "Strongly Agree" with the statements that are being read. ***Read three of the statements below related to practitioner willingness to try new therapies in general, reliance upon research or colleagues to guide new treatment practices, and attitudes about medication-assisted treatment. If you decide to use Option #1, instruct participants to stand on the virtual scaling ruler depending upon how they feel about the statement – from Strongly Disagree to Strongly Agree. For each statement, facilitate a discussion by asking participants to share their reasons or beliefs that impact where they stand on the scaling ruler. In a motivational interviewing style, you can also selectively ask participants what it would take to move their beliefs, values, or attitudes in either direction.*** ***Alternatively, if you decide to use Option #2, instruct participants to stand up depending upon how they feel about the statement – from Strongly Disagree to Strongly Agree. For each statement, facilitate a discussion by asking participants to share their reasons or beliefs that impact where they stand on the scaling ruler. In a motivational interviewing style, you can also selectively ask participants what it would take to move their beliefs, values, or attitudes in either direction.***

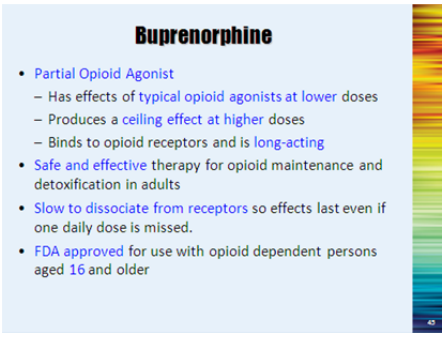
NOTES FOR SLIDE 43 CONTINUED FROM PREVIOUS PAGE	**Slide 43: Interactive Activity #1: Views on Medication-Assisted Treatment**  ***<u>Statements for the Activity (select 3 of the following 5 statements to read aloud):</u>*** 1. Use of medications for the treatment of prescription opioid addiction is merely swapping one addiction for another. 2. Medications are acceptable for a short time frame, but the person should be tapered off all medications as soon as possible. 3. For some people, treatment with medications alone will be sufficient. 4. Individuals who are addicted to prescription opioids are not as severely dependent as those individuals who are addicted to heroin. 5. Medications such as buprenorphine or methadone can help individuals move down a path of long-term recovery. ***<u>Sample Script:</u> Sally, when asked how you feel about the use of medications in the treatment of prescription opioid addiction, you indicated you are a 4 on the scale. Why are you a 4? Why are you a 4 instead of a 2? What would it take for you to move to a 6 on the scale?***



Slide 44: The Medication: Buprenorphine-Naloxone
(Transition Slide)

It is clear from the previously presented statistics that prescription opioid abuse is a significant problem in the United States.

In order to understand the results of the study using this medication with prescription opioid dependent adults, it is important that we understand how the medication (buprenorphine-naloxone) works. In the next section, we will look at the mechanism of action of this medication and issues pertaining to its efficacy, safety, and cost-effectiveness.



Slide 45: Buprenorphine

Buprenorphine is a partial opioid agonist. It has been shown to be safe and effective for the treatment of opioid addiction both as a maintenance agent and for use during withdrawal from opioids.

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

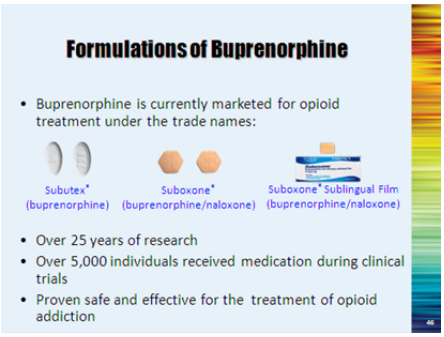
Buprenorphine's abuse potential is relatively low when compared with the abuse potential of full agonist *mu opioids.* Low doses of injected buprenorphine (such as 1 mg or less) produce minimal effects and are primarily identified as placebo-like in opioid dependent patients

Clinical trials have established the effectiveness of buprenorphine for the treatment of heroin addiction.

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.

NOTES FOR SLIDE 45 CONTINUED FROM PREVIOUS PAGE	**Slide 45: Buprenorphine** ***Additional Information for the Trainer(s):*** 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 46: Development of 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

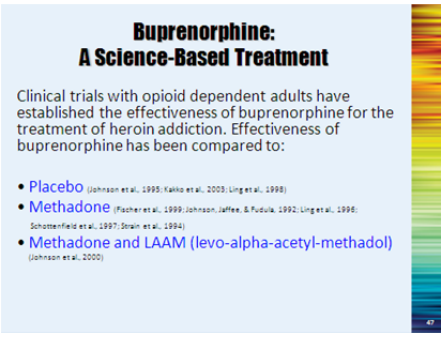
Suboxone® = a sublingual tablet containing both buprenorphine hydrochloride and naloxone hydrochloride in a 4:1 ratio

Reckitt Benckiser's exclusive rights expired in fall 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 U.S.

The basic pharmacology, pharmacokinetics, and efficacy of the combination product are the same as the mono-product. Buprenorphine-naloxone has a ceiling effect at higher doses, blocks the effects of other opioid agonists, binds strongly to the opioid receptor, and is long acting.

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 47: Buprenorphine: A Science-Based Treatment

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.

Buprenorphine's partial mu agonist properties make it mildly reinforcing, which encourages good patient adherence for regular medication ingestion.

Buprenorphine is a highly safe medication for both acute and long-term administration.

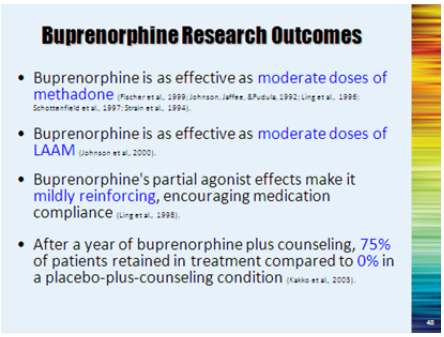
<u>References:</u>

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), 1337-47. (n=60)

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*, 2750–55. (n=162)

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. (n=150)

NOTES FOR SLIDE 47 CONTINUED FROM PREVIOUS PAGE	**Slide 47: Buprenorphine: A Science-Based Treatment**  References, continued: 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), 1290-97. (n=220) 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), 662-68. (n=40) 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*, 475-86. (n=736) 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*, 713-20. (n=116) 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*, 1025-30. (n=164)



Slide 48: 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., 60mg).

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, three-quarters of the patients receiving buprenorphine and counseling were still in treatment after one year. None of the placebo patients were retained.

<u>References: Bullet #1:</u>

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), 1337-47.

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*, 2750-55.

NOTES FOR SLIDE 48 CONTINUED FROM PREVIOUS PAGE	**Slide 48: Buprenorphine Research Outcomes**  References: Bullet #1, continued: 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*, 713-20. 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*, 1025-30. 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), 1290-97. 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*, 475-86. 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 randomised, placebo-controlled trial. *The Lancet, 361*(9358), 662-68.

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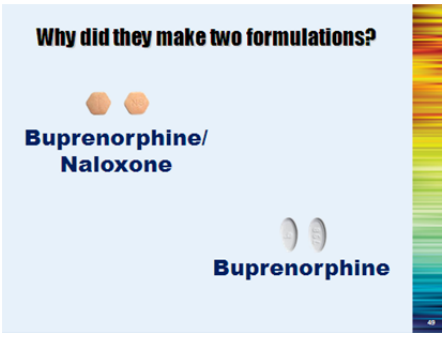
<td> 
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<td>Slide 49: Why did they make two formulations?

As was previously stated, the focus of marketing in the U.S. and the formulation used in the CTN studies is the buprenorphine-naloxone combination tablet. Understanding why this combination was made is critical.</td>
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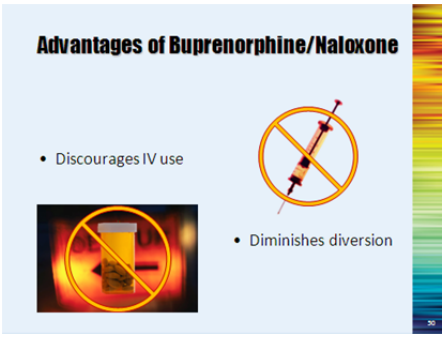
<td> 
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<td>Slide 50: Advantages of Buprenorphine-Naloxone

The buprenorphine-naloxone formulation has some advantages compared with the buprenorphine only formulation:
• 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.</td>
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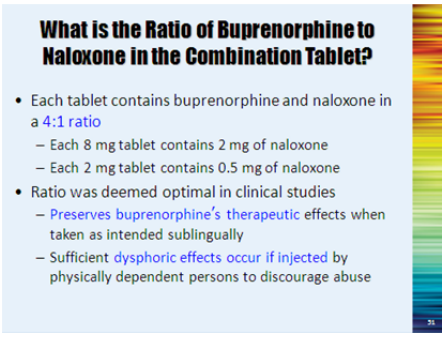
<td> 
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<td>Slide 51: What is the Ratio of Buprenorphine to Naloxone in the Combination Tablet?

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 patient (to discourage them from doing so).</td>
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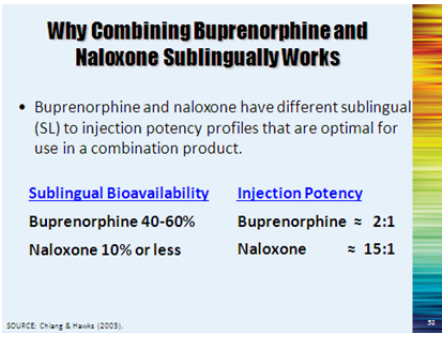


Slide 52: Why Combining Buprenorphine and Naloxone Sublingually Works

Digestive juices would kill buprenorphine's effects if it were to be swallowed. 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.

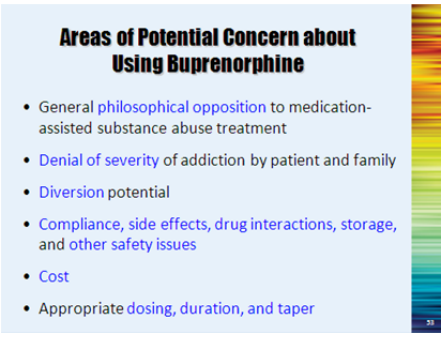
When taken under the tongue, the person receives approximately 40-60 percent of the buprenorphine available, but only 10% of the naloxone.

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

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

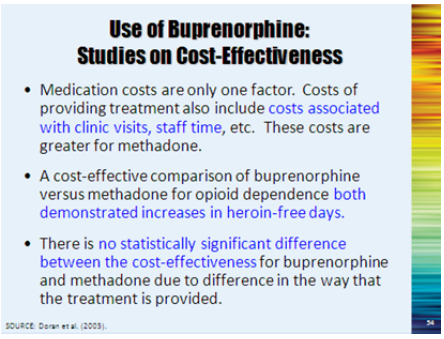
Reference:

Chiang, C.N, & Hawks, R.L., (2003). Pharmacokinetics of the combination tablet of buprenorphine and naloxone. *Drug and Alcohol Dependence, 70,* S39-47.



Slide 53: Areas of Potential Concern about Using Buprenorphine

Some issues that compound a physician's reluctance to prescribe buprenorphine include: general philosophical concerns among clinicians against medication-assisted treatment for substance use disorders; denial of severity of addiction by patient and/or family; poor medication compliance; and hampered ability to determine efficacy of medications due to denial, and poor compliance with both psychosocial treatment and the taking of medications.



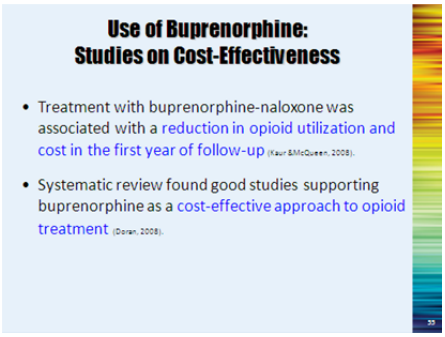
Slide 54: Use of Buprenorphine: Studies on Cost-Effectiveness

Much discussion has ensued 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.

Recently, research conducted on adult populations has demonstrated the utilization of buprenorphine is cost-effective across several indicators.

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 regimen that was tailored to the clinical need of the patients, with high maximum doses, using the marketed tablet formulation, under double-blind conditions.

NOTES FOR SLIDE 54 CONTINUED FROM PREVIOUS PAGE	**Slide 54: Use of Buprenorphine: Studies on Cost-Effectiveness** 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.  <u>Reference:</u> 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):* 295-302.  ***The subsequent two slides provide specific examples of the indicators that are referenced in bullet #2 (e.g., heroin-free days, lower crime-related costs, etc.).***



Slide 55: Use of Buprenorphine: Studies on Cost-Effectiveness

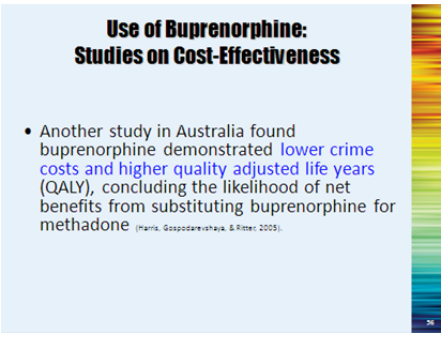
Another study conducted by Kaur & McQueen (2008) found that the treatment with buprenorphine-naloxone was associated with a reduction in opioid utilization and cost in the first year of follow-up.

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.

References:

Doran, C. M. (2008). Economic evaluation of interventions to treat opiate dependence: a review of the evidence. *Pharmocoeconomics, 26(5),* 371-93.

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. *Journal of Managed Care Pharmacy, 14(2),* 186-94.



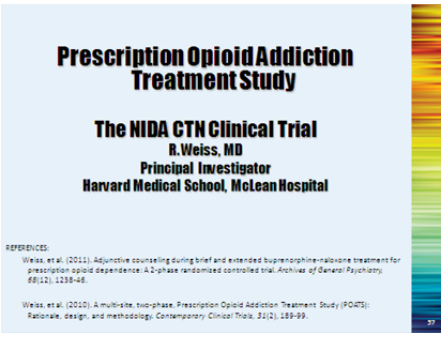
Slide 56: Use of Buprenorphine: Studies on Cost Effectiveness

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).

The researchers found that buprenorphine demonstrated lower crime costs and higher quality adjusted life years.

Reference:

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. *Pharmocoeconomics, 23(1),* 77-91.



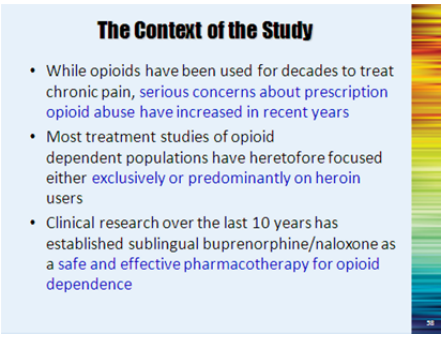
Slide 57: Prescription Opioid Addiction Treatment Study
(Transition Slide)

The next series of slides will present information on the NIDA CTN clinical trial conducted by Dr. Roger Weiss and colleagues of adjunctive counseling during brief and extended buprenorphine-naloxone treatment for prescription opioid dependence.

References:

Weiss, et al. (2011). Adjunctive counseling during brief and extended buprenorphine-naloxone treatment for prescription opioid dependence: A 2-phase randomized controlled trial. *Archives of General Psychiatry, 68*(12), 1238-46.

Weiss, et al. (2010). A multi-site, two-phase, Prescription Opioid Addiction Treatment Study (POATS): Rationale, design, and methodology. *Contemporary Clinical Trials, 31*(2), 189-99.



Slide 58: The Context of the Study

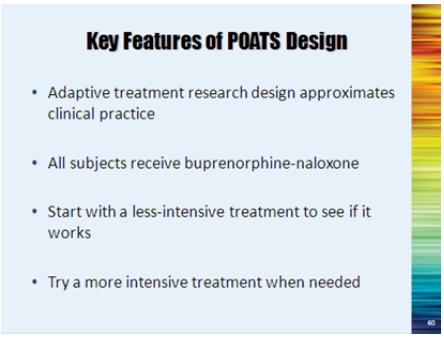
Until POATS, no randomized clinical trials examined treatments for prescription opioid dependence, despite its increasing prevalence.

Slide 59: The Prescription Opioid Addiction Treatment Study (POATS)

The **primary objective** of POATS was to determine whether the addition of individual drug counseling to the prescription of buprenorphine-naloxone along with Standard Medical Management (SMM) for subjects dependent on prescription opioids improves outcome both during (a) an initial four-week treatment with taper and (b) a 12-week stabilization treatment for those who do not respond successfully to the initial treatment with taper.

Subjects underwent an initial four-week buprenorphine-naloxone outpatient treatment with taper, and were randomized to SMM or SMM+ODC, which consisted of SMM plus twice weekly individual outpatient drug counseling.

After the initial treatment with taper, participants who were thus far successful were followed for eight weeks to assess success or failure. Initial treatment failures were eligible for treatment in phase 2. Phase 2 consisted of a 12-week outpatient stabilization treatment with buprenorphine-naloxone, plus random assignment to SMM or SMM+ODC, followed by a four-week taper and eight weeks of follow-up.



Slide 60: Key Features of POATS Design

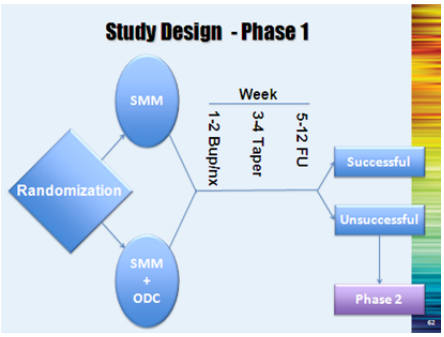
An adaptive treatment research design is used to identify a treatment strategy for a disorder, including the optimal response to an initial treatment failure. In the present study, the response (successful or unsuccessful) to initial brief buprenorphine-naloxone treatment (phase 1) determined whether patients would require extended buprenorphine-naloxone treatment (phase 2).

Slide 61: The Prescription Opioid Addiction Treatment Study (POATS): Design

POATS was a multi-site, randomized clinical trial that used a 2-phase adaptive treatment research design. Brief treatment (phase 1) included 2-week buprenorphine-naloxone stabilization, 2-week taper, and 8-week post-medication follow-up. Subjects with successful opioid use outcomes exited the study; unsuccessful subjects entered phase 2: extended (12-week) buprenorphine-naloxone treatment, 4-week taper, and 8-week post-medication follow-up.

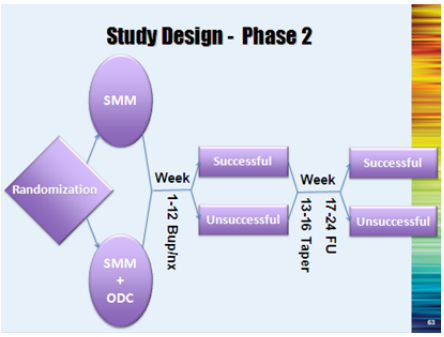
The study compared outcomes for individuals receiving standard medical management (SMM) and those receiving manual-based opioid dependence counseling. The SMM visits encompassed strategies such as assessing cravings and recommending abstinence and self-help group participation. The more extensive opioid dependence counseling from behavioral health professionals employed relapse prevention and 12-step strategies.

Standard medical management (SMM) in the study was considered by the investigators to be “pretty good counseling.” Doctors in the community usually see patients only once a month. In POATS, doctors saw patients for 15-20 minutes each week.



Slide 62: Study Design – Phase 1

The phase 1 study design was stratified by the presence or absence of a history of heroin use and current chronic pain. Standard medical management (SMM) was 2 visits for week 1; 1 visit/week for weeks 2-4; and biweekly visits for weeks 5-8. Enhanced medical management (SMM+ODC) was 2 visits/week for weeks 1-4 and biweekly visits for weeks 5-8. The buprenorphine-naloxone dose ranged from 8-32 mg/day. The phase 1 primary end point was the completion of week 12 with self-reported opioid use on no more than 4 days in a month, absence of 2 consecutive opioid-positive urine test results, no additional substance use disorder treatment (other than self-help), and no more than 1 missing urine sample.

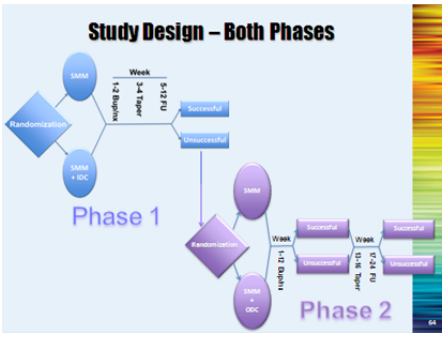


Slide 63: Study Design – Phase 2

Unsuccessful subjects in phase 1 were invited into phase 2 as soon as successful outcome was no longer attainable according to the protocol.

The phase 2 study design was stratified by the phase 1 counseling condition, specifically SMM or SMM+ODC. Standard medical management (SMM) was 2 visits for week 1 and 1 visit/week for weeks 2-16. Enhanced medical management (SMM+ODC) was 2 visits/week for weeks 1-6 and 1 visit/week for weeks 7-12. The buprenorphine-naloxone dose ranged from 8-32 mg/day. The phase 2 primary end point was abstinence from opioid use during week 12 (the final week of buprenorphine-naloxone stabilization) and during at least 2 of the previous 3 weeks (weeks 9-11). The phase 2 secondary end point was abstinence from opioid use during week 24 and during at least 2 of the previous 3 weeks (weeks 21-23).

(After the 12-week BUP/NX stabilization treatment, participants in both groups were tapered off BUP/NX over four weeks (weeks 13-16) while receiving SMM only).



Slide 64: Study Design – Both Phases

This slide depicts both phases of POATS.

Additional Information for the Trainer(s):
870 individuals were assessed for eligibility. Of those, 222 did not meet the inclusion criteria, leaving ***653 individuals randomized in phase 1***.

Phase 1, SMM+ODC:
329 assigned
- 19 successful outcomes
- 88 lost to follow-up
- 2 investigator-initiated termination

220 eligible for phase 2
11 refused
38 lost contact

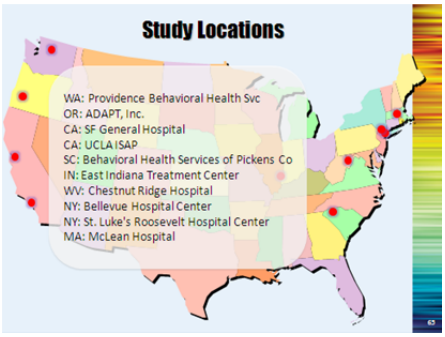
Phase 1, SMM:
324 assigned
- 24 successful outcomes
- 75 lost to follow-up
- 0 investigator-initiated termination

225 eligible for phase 2
9 refused
27 lost contact

360 randomized in phase 2

Phase 2, SMM+ODC:
180 assigned
- 19 lost to follow-up before week 13
- 0 discontinued intervention (jailed)

Phase 2, SMM:
180 assigned
- 18 lost to follow-up before week 13
- 1 discontinued intervention (jailed)

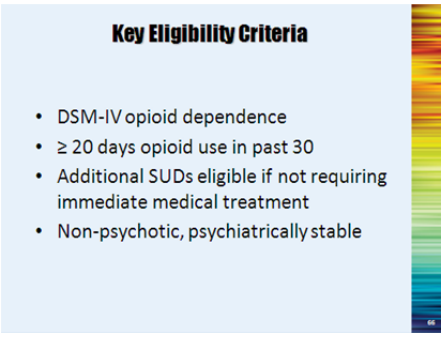


Slide 65: Study Locations

Move forward and site locations will appear one at a time.

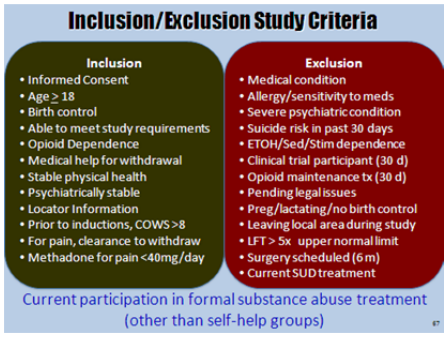
This slide shows the sites that participated in the clinical trial. There were a total of 10 sites across the United States.

Additional Information for the Trainer(s):
The CTN works to ensure diversity among participating sites (geography, client demographics, etc.) to maximize generalizability. CTN Nodes self-select community treatment programs for participation in a protocol based on interest in the protocol and the ability to recruit appropriate participants into the study (i.e., clients served by the agency are representative of the target population for the study).



Slide 66: Key Eligibility Criteria

The two-phase outpatient study included males and females 18 years of age or older, seeking detoxification from prescription opioid dependence in the absence of chronic pain severe enough to require ongoing opioid therapy or an acute pain event within the past six months. For subjects receiving opioids for pain, the study medical clinician consulted with the subject's prescribing physician to ensure that the subject was medically stable enough to enter the trial (e.g., the subject does not have a malignant tumor causing the pain). Subjects who used prescription opioids by injection were included as long as they had never injected heroin. Subjects had to meet the DSM-IV criteria for current dependence on prescription opioids. While physiologic features are essential, DSM-IV dependence requires more than just tolerance and withdrawal to be present; must have behavioral symptoms, as well. Physical dependence was not sufficient for study participation. Subjects were excluded if they required ongoing opioid therapy for pain.



Slide 67: Inclusion/Exclusion Study Criteria

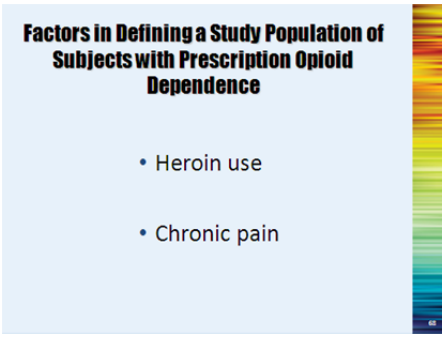
Move forward to reveal a series of inclusion and exclusion criteria one at a time. As each criterion is highlighted, additional information or a definition will appear at the bottom of the slide in blue text.

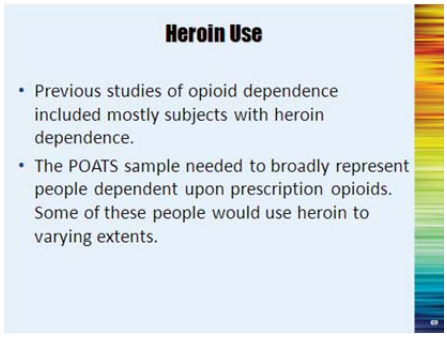
Inclusion and exclusion criteria are selected by the investigators to maximize generalizability of the study participants to the general population, and to ensure maximum safety for study participants.

Inclusion criteria

1) Ability to read, understand, and provide written informed consent
2) Age ≥18
3) If female and of childbearing potential, agrees to use an acceptable method of birth control throughout study
4) Ability to meet study requirements (i.e., can attend weekly visits, able to take medications, etc.)
5) Meets DSM-IV criteria for current opioid dependence (not simply physically dependent and taking opioids for pain as prescribed)
6) Current physical dependence on opioids (using prescription opioids ≥20 days/month) and need for medical assistance for opioid withdrawal
7) Good general health or, if requires ongoing medical/psychiatric treatment (whether currently in such treatment or not), participant is under the care of a physician willing to continue participant's medical management and to cooperate with study site investigators
8) Non-psychotic and psychiatrically stable, in the opinion of the study investigator

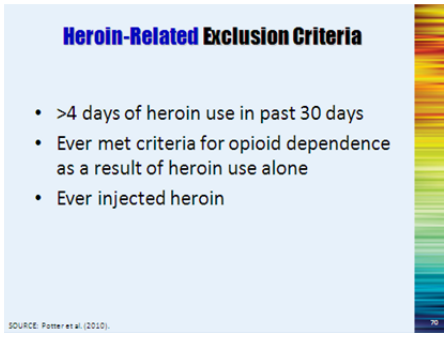
NOTES FOR SLIDE 67 CONTINUED FROM PREVIOUS PAGE	**Slide 67: Inclusion/Exclusion Study Criteria** **<u>Inclusion criteria, continued</u>** 9) Willingness to provide locator information 10) Prior to induction, participant is in opioid withdrawal (COWS scale >8) 11) For participants receiving opioids for pain, clearance from their prescribing physician to be withdrawn from their prescribed opioids 12) For participants receiving methadone for pain (those currently receiving methadone treatment for opioid dependence are excluded), dose is ≤40 mg/day **<u>Exclusion criteria</u>** 1) A medical condition that would make participation medically hazardous 2) A known allergy or sensitivity to buprenorphine or naloxone 3) An acute severe psychiatric condition or psychosis 4) Participant has been a suicide risk within the past 30 days 5) Dependence on alcohol, sedative-hypnotics or stimulants, and requiring immediate medical attention 6) Participation in another investigational drug study within the last 30 days 7) Participation in methadone or buprenorphine maintenance treatment for opioid dependence within 30 days of study enrollment 8) A current or pending legal status that would make the participant unlikely to remain in the local area for the duration of the study

NOTES FOR SLIDE 67 CONTINUED FROM PREVIOUS PAGE	**Slide 67: Inclusion/Exclusion Study Criteria** **<u>Exclusion criteria, continued</u>** 9) If female, participant is pregnant, lactating, or unwilling to follow study-required measures for pregnancy prevention 10) Inability to remain in the local area for the duration of the study 11) Liver function tests >5 times the upper limit of normal 12) Surgery scheduled within the next 6 months that would preclude participation during the active treatment phase of the study 13) Current participation in formal substance abuse treatment (other than self-help groups)
	**Slide 68: Factors in Defining a Study Population of Subjects with Prescription Opioid Dependence** Heroin use and chronic pain were used as stratification variables on the phase 1 primary end points, so secondary analyses could be performed on the phase 1 outcomes to see if there was a relationship between the outcomes and the one or both of the stratification factors. ***Additional Information for the Trainer(s):*** For phase I, the randomization was stratified by whether or not the subject had ever used heroin, and whether or not the subject had current chronic pain. Whereas for phase 2, it was stratified by the treatment received in phase I (SMM+ODC or SMM). To keep the sequencing of treatment assignment confidential, block size was not revealed to the investigators.



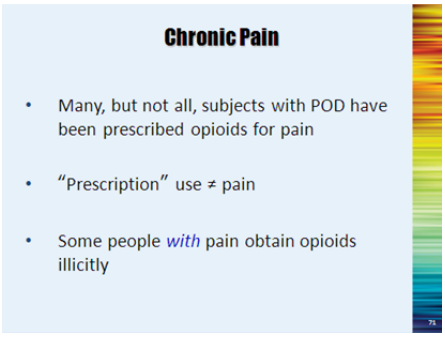
Slide 69: Heroin Use

As was previously stated, most of the previous studies on opioid dependence have primarily included individuals with a history of heroin dependence, with a smaller number presenting with a history of prescription opioid dependence. Because the goal of POATS was to investigate treatment options for prescription opioid users specifically, the subject population needed to include primary of prescription opioid abusers. The study investigators recognized, however, that some prescription opioid users may also abuse heroin from time to time.



Slide 70: Heroin-Related Exclusion Criteria

Potential study participants were excluded if they used heroin more than 4 days in the past month; had a lifetime opioid dependence diagnosis due to heroin alone; and had ever injected heroin.



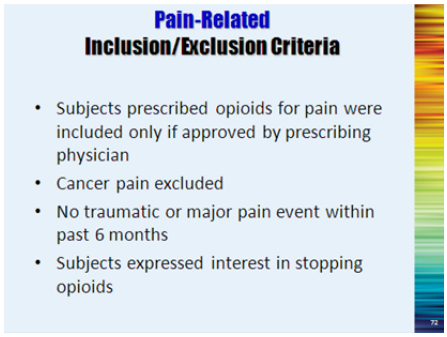
Slide 71: Chronic Pain

The presence of "chronic pain" was operationalized by a 'yes' answer to the first question of the Brief Pain Inventory (whether you have pain beyond usual aches and pains) AND a duration of pain of at least three months**.**

Additional Information for the Trainer(s):
Chronic pain is widely believed to represent disease itself. It can be made worse by environmental and psychological factors. Chronic pain persists over a longer period of time than acute pain, and is resistant to most medical treatments. It can, and often does, cause severe problems for patients. A person may have two or more co-existing chronic pain conditions at any given time.

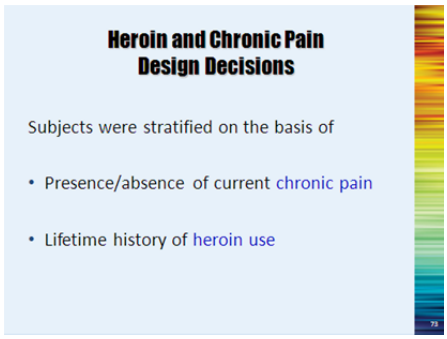
A dilemma exists with regards to pain management. It is critical to accurately assess and diagnose acute and chronic pain, and provide the necessary and effective analgesia, if needed. There is a need to accurately diagnose disease and provide effective pain management. Some illnesses have no clearly explainable pathophysiology, but are frequently cited as reasons for pain syndromes needing medication treatment(s), including: headache; low back pain; pelvic pain; arthritis; Fibromyalgia; and Chronic Fatigue Syndrome. A misunderstanding and mismanagement of pain may contribute to abuse of pain medications.

NOTES FOR SLIDE 71 CONTINUED FROM PREVIOUS PAGE	**Slide 71: Chronic Pain** <u>Pain Control and Addiction</u>: "Pseudoaddiction" Presence of drug-seeking behavior in context of inadequate pain control Behavior stops with adequate pain relief Physical dependence with continued use, withdrawal syndrome produced by rapid dose reduction; occurs via neuroadaptation *Not synonymous with addiction* With regards to diagnosing addiction in opioid-maintained pain patients, there are no validated diagnostic criteria for addiction in pain patients; only "at risk" behaviors, including: lack of control; compulsive use; continued use despite harm; increased craving; and psychiatric symptoms. To identify "at risk" patients, a clinician might use: patient's history; screening instruments; behavioral checklists; and therapeutic interactions. With regards to early intervention for prescription drug abuse, health care providers should: (1) screen patients w/ abuse symptoms; (2) be aware of increases in medication amount needed; and (3) frequent, unscheduled refill requests. Pharmacists can: (1) provide clear information about proper medication use, effects and danger of drug interactions; and (2) prevent prescription fraud by looking for false prescription forms. Patients can: (1) provide complete medical history; (2) describe reason for the visit to ensure proper medication; (3) avoid increasing or decreasing doses or abruptly discontinuing prescription use without permission from a physician.



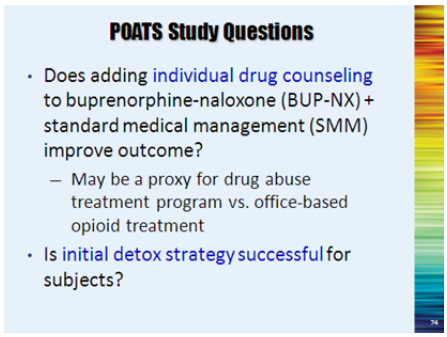
Slide 72: Pain-Related Inclusion/Exclusion Criteria

Potential study participants were excluded if they had experienced a major pain event in the past six months; had cancer-related pain; and were prescribed methadone (>40mg/day) for pain. Potential participants needed to express an interest in stopping prescription opioid use to be enrolled in POATS.



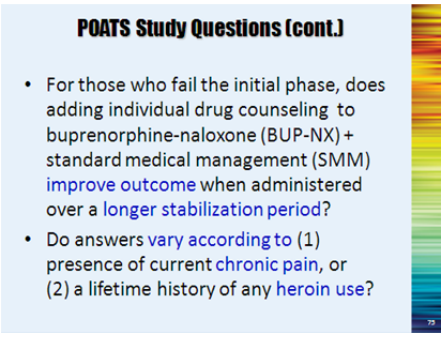
Slide 73: Heroin and Chronic Pain Design Decisions

The randomization for phase 1 was within site and was stratified with respect to two factors: 1) whether or not the subject had ever used heroin; and 2) whether or not the subject currently had chronic pain, as previously defined on slide 71.



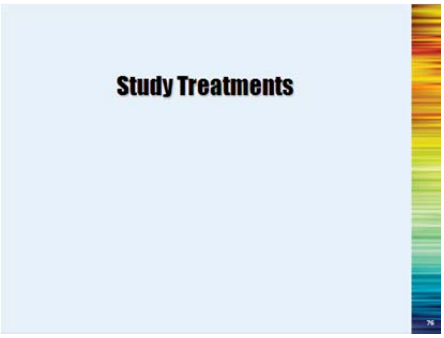
Slide 74: POATS Study Questions

The **primary research question** for the study was: What benefit does SMM+ODC offer over SMM in (a) a short-term treatment paradigm (a four-week buprenorphine-naloxone treatment with taper) and (b) a longer-term treatment paradigm (12 weeks of a stabilization dose of buprenorphine-naloxone) for subjects who have not responded successfully to the initial short-term buprenorphine-naloxone treatment with taper?



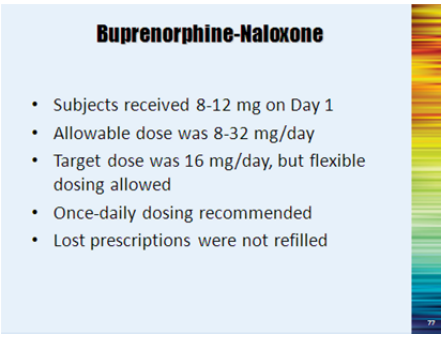
Slide 75: POATS Study Questions (cont.)

Secondary research questions included: (1) For those who failed phase 1, did the addition of individual opioid drug counseling to buprenorphine-naloxone and SMM improve outcome when administered over a longer stabilization period (phase 2)?; and (2) Were there subject characteristics that predict the likelihood of success in Phase 1, such as heroin use or chronic pain?



Slide 76: Study Treatments
(Transition Slide)

The next set of slides describes, in more detail, the study treatments, including buprenorphine-naloxone, standard medical management, and individual opioid drug counseling.



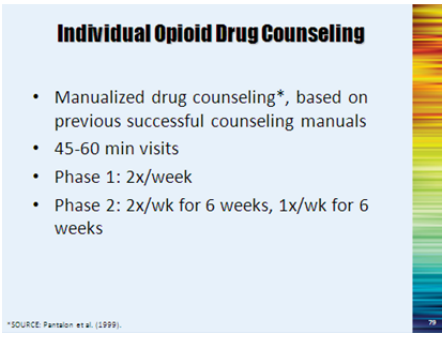
Slide 77: Buprenorphine-Naloxone

Subjects with a score greater than eight on the Clinical Opiate Withdrawal Scale (COWS) were inducted onto sublingual buprenorphine-naloxone and were dispensed buprenorphine-naloxone for once-daily daily dosing at weekly SMM visits. Patients received 4-12 mg (in 4-mg doses) on the induction day, depending on their initial response to buprenorphine-naloxone. At each subsequent SMM visit, the study physician could adjust the buprenorphine-naloxone does in increments of up to 8mg/week; the dose was adjusted for opioid use, withdrawal symptoms, adverse effects, and craving but not for pain. The allowable dose was 8-32 mg/day, consistent with practice guidelines. Non-opioid comfort medications (e.g., loperamide for diarrhea) were permitted during medication tapers.

Slide 78: Standard Medical Management

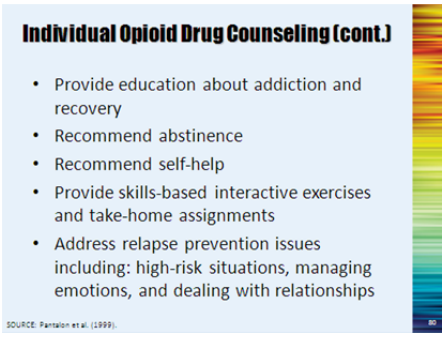
Manual-based Standard Medical Management (SMM), which has previously demonstrated efficacy, was provided to all the subjects by physicians certified to prescribe buprenorphine. During the initial session in each phase (45-60 minutes in phase 1 and 30-60 minutes in phase 2), the physician reviewed the patient's medical, psychiatric, and substance use problems; recommended abstinence; and referred the subject to self-help groups. In subsequent 15- to 20-minute visits, the physician assessed substance use, craving, and buprenorphine-naloxone response; recommended abstinence and self-help participation; and prescribed buprenorphine-naloxone.

SMM represents a higher level of care than is routinely provided to patients receiving medical services for opioid addiction.



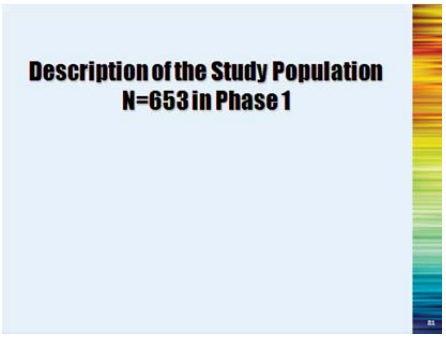
Slide 79: Individual Opioid Drug Counseling

In addition to SMM, half of the subjects were randomly assigned to receive manual-based individual opioid drug counseling, delivered in 45-60 minute sessions by trained substance abuse or mental health professionals. The counseling was based on drug counseling manuals with demonstrated efficacy, modified for this study.



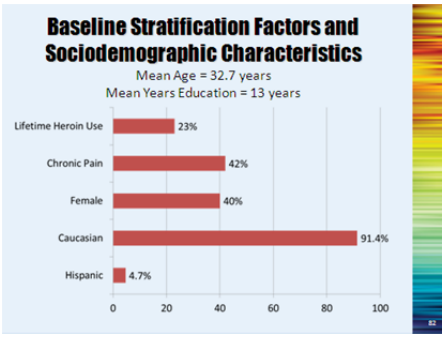
Slide 80: Individual Opioid Drug Counseling (cont.)

Counselors educated subjects about addiction and recovery, recommended self-help groups, and emphasized lifestyle change. Using a skills-based format with interactive exercise and take-home assignments, the counseling covered a wider range of relapse prevention issues in greater depth than did SMM, including coping with high-risk situations, managing emotions, and dealing with relationships.



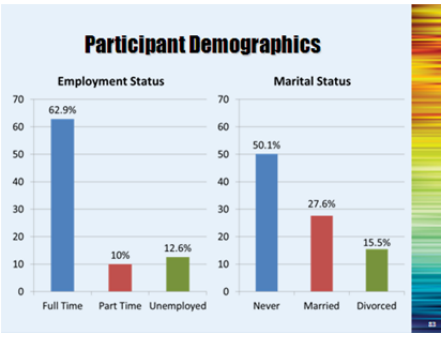
Slide 81: Description of Study Population
(Transition Slide)

The next series of slides presents data to describe the study population.



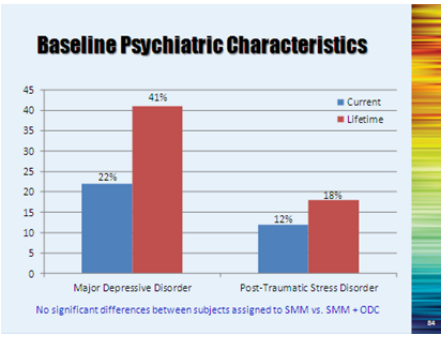
Slide 82: Baseline Stratification Factors and Sociodemographic Characteristics

The sociodemographic and clinical characteristics of the subjects enrolled did not differ between treatment groups. About one in four (23%) of all subjects reported lifetime heroin use and about four in 10 (42%) reported current chronic pain. Forty percent of the subjects were female, and approximately 90% were Caucasian. Less than 5% were Hispanic.



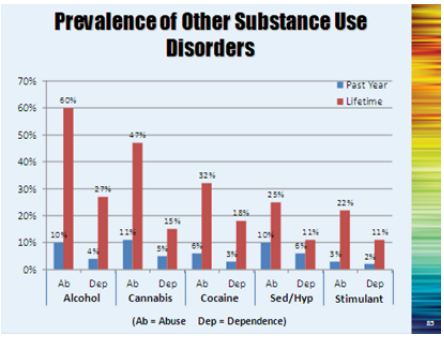
Slide 83: Participant Demographics

The POATS sample was well employed, with nearly two-thirds reporting current full-time employment. About half of the sample was never married.



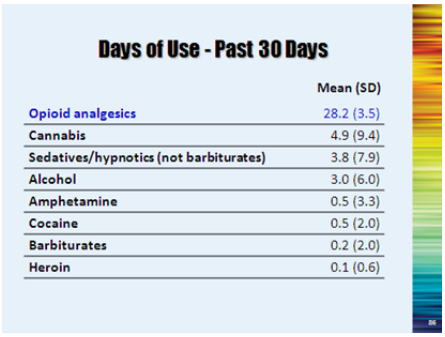
Slide 84: Baseline Psychiatric Characteristics

The Composite International Diagnostic Interview (CIDI) was administered at baseline to diagnose opioid dependence, other substance-related disorders, major depressive disorder, and post-traumatic stress disorder. About 40% of subjects reported lifetime major depressive disorder, followed by 22% reporting current major depressive disorder. The prevalence of post-traumatic stress disorder (PTSD) was lower, with 18% reporting lifetime PTSD and 12% reporting current PTSD.



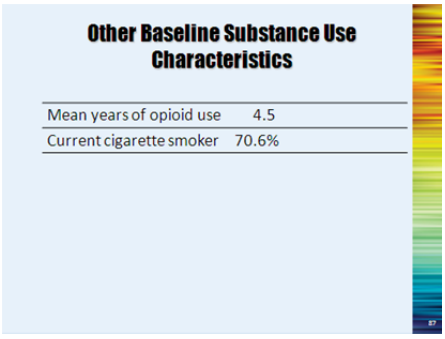
Slide 85: Prevalence of Other Substance Use Disorders

Urine samples for drugs of abuse (including the opioid analgesics oxycodone, hydrocodone, hydromorphone, morphine, codeine, propoxyphene, and methadone) and self-reports of substance use were collected weekly during treatment and biweekly during follow-up; a calendar-based interview technique reviewed each day since the previous visit. With regards to the prevalence of other substance use disorders, subjects were most likely to report lifetime alcohol (60%), cannabis (47%), or cocaine (32%) dependence. Rates of past year prevalence of other types of SUDs were much lower than reported lifetime rates.



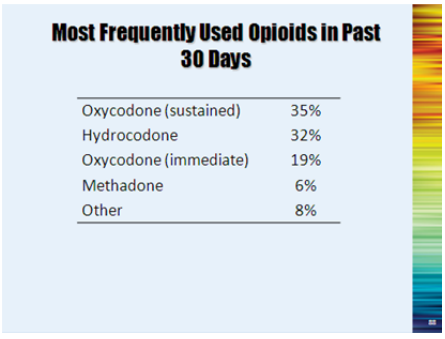
Slide 86: Days of Use – Past 30 Days

Overall, subjects tended to use prescription opioids almost daily, but not much else. The use of cannabis, sedatives/hypnotics, and alcohol was reportedly used in a range of 3-5 days in the past month.



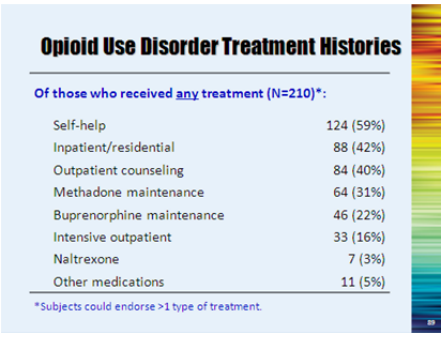
Slide 87: Other Baseline Substance Use Characteristics

Subjects reported an opioid use history of four and one-half years; 71% reported current cigarette smoking.



Slide 88: Most Frequently Used Opioids in Past 30 Days

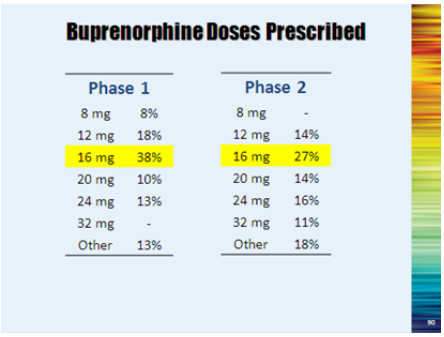
Subjects were most likely to report recent use of oxycodone (sustained release), hydrocodone, or oxycodone (immediate release).



Slide 89: Opioid Use Disorder Treatment Histories

Of the 634 subjects who entered into phase 1, 210 (33%) reported a history of previous treatment for an opioid use disorder.

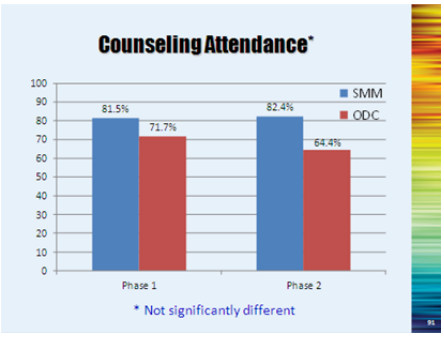
Of those who reported a history of any treatment for an opioid use disorder (N=210), individuals were most likely to report a history of attending self-help groups (59%), followed by inpatient/residential treatment (42%), outpatient counseling (40%), or methadone maintenance therapy (31%).



Slide 90: Buprenorphine Dose Prescribed

The most frequently prescribed maximum dose of buprenorphine-naloxone in phase 1 was 16 mg, followed by 12 mg, 24 mg, 20 mg, 8 mg, and other doses. In phase 2, 16 mg and 24 mg were the most frequently prescribed maximum doses, followed by 12 mg, 20 mg, 32 mg, and other doses.

Medication adherence was measured by self-report, which was aided by pill count. Adherence was high; 95.5% and 98.1% of doses were reported to be taken as prescribed during phases 1 and 2, respectively.



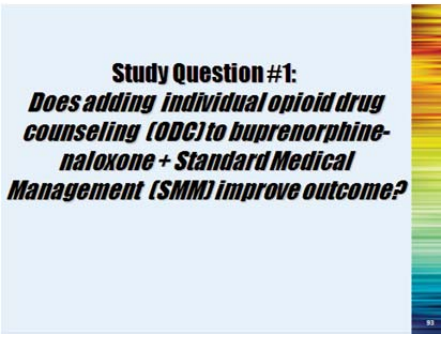
Slide 91: Counseling Attendance

In Phase 1, patients attended a mean of 4.5 (standard deviation=1.5) SMM visits (**81.5%** of the maximum possible number of visits) and 6.6 (sd=3.5) ODC sessions (**71.7%** of maximum possible); In Phase 2, patients attended a mean of 14.0 (sd=4.2) SMM visits (**82.4%** of maximum), and 11.6 (sd=5.2) ODC sessions (**64.4%** of maximum).

Based on Wilcoxon rank sum tests, **attendance at SMM visits did not vary by counseling condition in either phase** (4.4, sd=1.5 vs 4.5, sd=1.5; z=1.24, p=.39 during Phase 1; and 14.1, sd=4.4 vs 13.9, sd=4.0; z=.86, p=.21 during Phase 2; for SMM+ODC vs. SMM respectively).

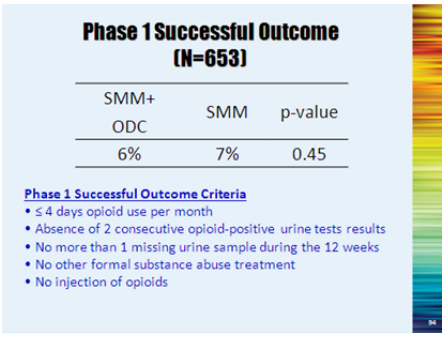
Slide 92: Results
(Transition Slide)

For both study phases, the investigators specified dichotomous successful outcomes as a priori primary end points in each phase. In both phases, the definition of "successful outcome" was based on specifying a clinically meaningful end point that would guide a treating physician in deciding whether to continue with the current treatment strategy or change course.



Slide 93: Study Question #1: Does adding individual opioid drug counseling (ODC) to buprenorphine-naloxone + Standard Medical Management (SMM) improve outcome?

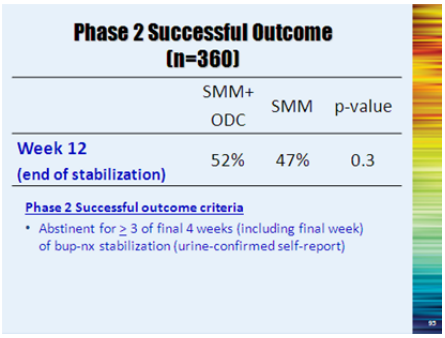
As a refresher, the **overall research question** for the study is: What benefit does EMM offer over SMM a) in a short-term treatment paradigm (a four-week buprenorphine-naloxone treatment with taper) and b) in a longer-term treatment paradigm (12 weeks of a stabilization dose of buprenorphine-naloxone) for subjects who have not responded successfully to the initial short-term buprenorphine-naloxone treatment with taper?



Slide 94: Phase 1 Successful Outcome

In phase 1, successful outcome was defined as completing week 12 with self-reported opioid use on no more than 4 days in a month, absence of 2 consecutive opioid-positive urine test results, no additional substance use disorder treatment (other than self-help), and no more than 1 missing urine sample during the 12 weeks. Consistent with the adaptive treatment research design, subjects who were unsuccessful in phase 1 became immediately eligible for phase 2 even if they had not completed phase 1.

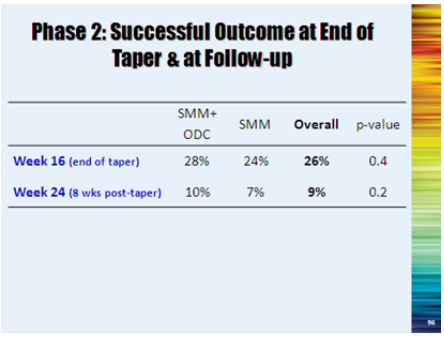
Overall, 43 of 653 subjects (6.6%) had successful outcomes with brief buprenorphine-naloxone treatment in phase 1, with no difference in success rates between those receiving SMM alone (7%) and those receiving SMM+ODC (6%).



Slide 95: Phase 2 Successful Outcome

In phase 2, successful outcome was defined as abstaining from opioids during week 12 (the final week of buprenorphine-naloxone stabilization) and during at least 2 of the previous 3 weeks (weeks 9-11). The definition of successful outcome in the 2 phases differed slightly because the study was designed to facilitate rapid transition from phase 1 to phase 2 for subjects returning to opioid use. Unlike in phase 2, unsuccessful patients ended phase 1 at different times, by design.

While only 6.6% of subjects had successful outcomes in phase 1, 49.2% of subjects were successful in phase 2 (extended buprenorphine-naloxone treatment). No differences in outcome based on the extent of counseling received were observed in either phase.

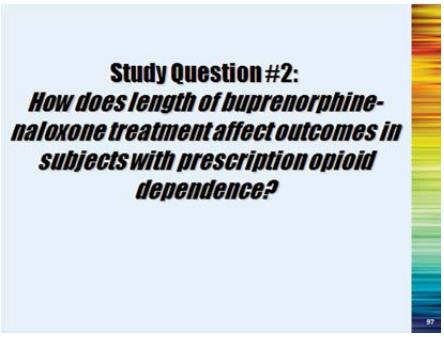


Slide 96: Phase 2: Successful Outcome at End of Taper & at Follow-up

A planned secondary outcome, successful outcome at week 24, that is, 8 weeks after completion of the phase 2 buprenorphine-naloxone taper, was defined the same as at week 12 of phase 2, that is, abstinence from opioids during week 24 and at least 2 of the3 previous 3 weeks.

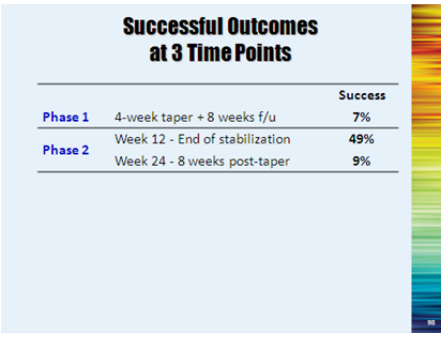
In phase 2, subjects' success rate 8 weeks post completion of the medication taper was 9%.

While there was no difference seen in level of counseling, it is important to remember that the lowest level of counseling (SMM) involved a significant amount of intervention. There was no counseling condition that matched the current standard of care seen in typical in opioid treatment programs.



Slide 97: Study Question #2: How does length of buprenorphine-naloxone treatment affect outcomes in subjects with prescription opioid dependence?

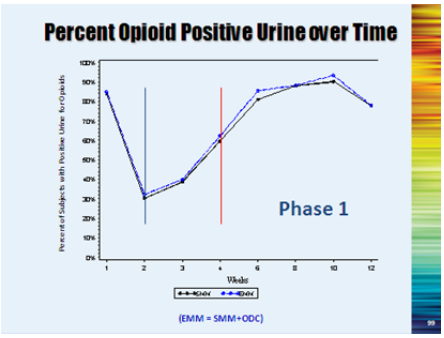
Study question #2 pertained to whether the length of buprenorphine-naloxone treatment affected outcomes.



Slide 98: Successful Outcomes at 3 Time Points

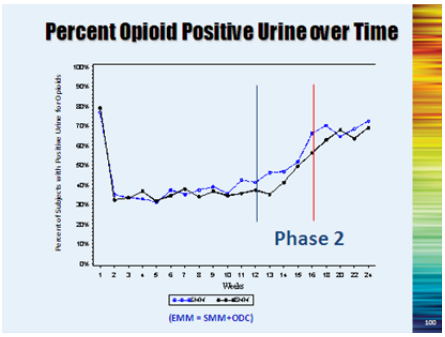
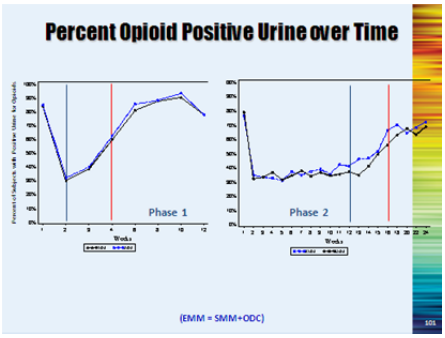
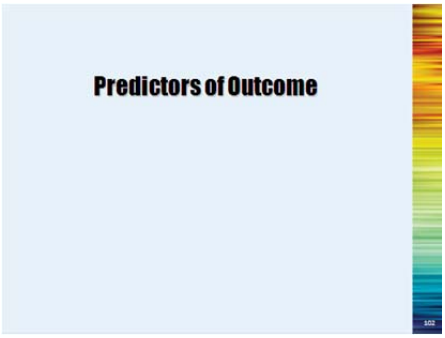
Overall, 43 of 653 patients (**6.6%**) had successful outcomes with brief buprenorphine-naloxone treatment in phase 1, with no difference in success rates between those receiving SMM along and those receiving SMM+ODC. In contrast, **49.2%** of subjects (177 of 360) attained successful outcomes in extended treatment (phase 2) while still taking buprenorphine-naloxone (week 12). As in phase 1, there was no difference between counseling conditions. Overall success rates 8 weeks after completing the buprenorphine-naloxone taper in phase 2 (week 24) dropped to **8.6%** (31 of 360 subjects), again with no differences between counseling conditions.

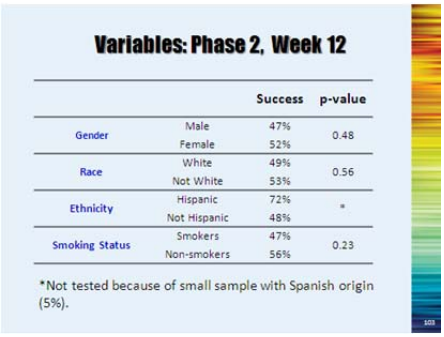
During phase 2, subjects were considerably more likely to attain success while continuing treatment with buprenorphine-naloxone than 8 weeks after completing the buprenorphine-naloxone taper, controlling for counseling condition (49.2% vs. 8.6%, $p<0.001$).



Slide 99: Percent Opioid Positive Urine over Time (Phase 1)

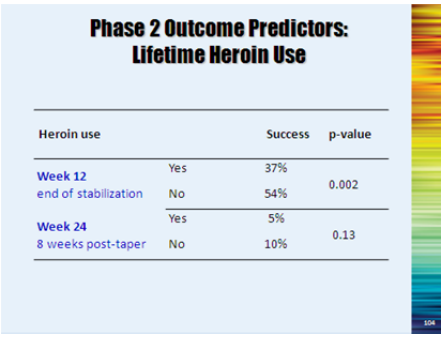
Here, the phase 1 results regarding the percentage of opioid positive urines over time presented graphically. The dark blue horizontal line (week 2) shows when the phase 1 taper began, and the red horizontal line (week 4) shows when phase 1 ended. Opioid-positive urine test results were lowest during weeks 2-3, and rebounded to the pre-study levels in the weeks following the phase 1 buprenorphine-naloxone taper.

	**Slide 100: Percent Opioid Positive Urine over Time (Phase 2)** Opioid-positive urine test results in phase 2 were significantly higher during the combined taper and post-taper periods (weeks 13-24) than while maintained on buprenorphine-naloxone during weeks 1 to 12 (58.1% vs. 39.1%, p<0.001).
	**Slide 101: Percent Opioid Positive Urine over Time (Both Phases)** This slide presents a side-by-side comparison of the previous two slides (phase 1 vs. phase 2 percentage positive urine test results).
	**Slide 102: Predictors of Outcome** ***(Transition Slide)*** This next set of slides presents data pertaining to covariates/predictors of outcome, specifically for phase 2.



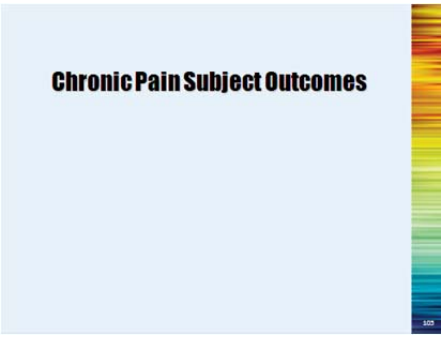
Slide 103: Variables: Phase 2, Week 12

Although none of the following differences were found to be statistically significant, females were slightly more likely than males to be successful at week 12 of phase 2; non-white subjects were slightly more likely to be successful than whites; and non-smokers were slightly more likely than smokers to be successful.



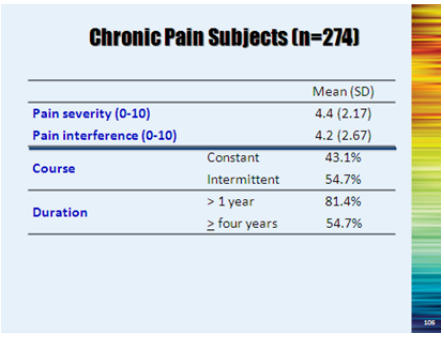
Slide 104: Phase 2 Outcome Predictors: Lifetime Heroin Use

Subjects with any lifetime heroin use (n=100) were less likely than non-heroin users (n=260) to have successful phase 2 outcomes while receiving buprenorphine-naloxone (37% vs. 54%, p=0.002). A history of any heroin use did not affect phase 1 outcomes.



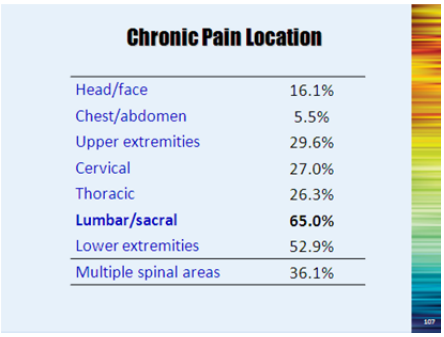
Slide 105: Chronic Pain Subject Outcomes
(Transition Slide)

The next set of slides presents data pertaining to the subjects reporting current chronic pain.



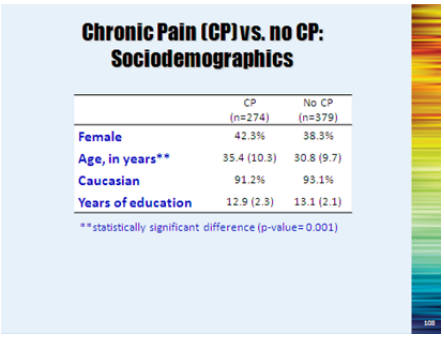
Slide 106: Chronic Pain Subjects (n=274)

Pain intensity and pain-related interference with life functioning were assessed via self-report at baseline and monthly using the Brief Pain Inventory-Short Form. Patients were designated at baseline as having current chronic pain if they reported pain "other than everyday kinds of pain," excluding withdrawal-related pain, for at least three months. The mean pain severity level (on a scale of 1 to 10) among chronic pain subjects was 4.4, and the mean pain interference level was 4.2. Chronic pain subjects were more likely to report an intermittent course of pain, and more than 50% reported chronic pain durations of four or more years.



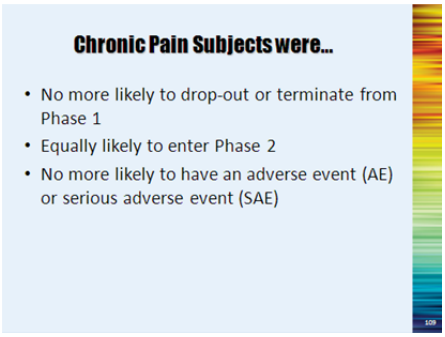
Slide 107: Chronic Pain Location

The most commonly reported chronic pain locations were in the lower back (65%), lower extremities (53%), or upper extremities (30%). More than a third (36%) of chronic pain subjects reported pain in multiple spinal areas.



Slide 108: Chronic Pain (CP) vs. no CP: Sociodemographics

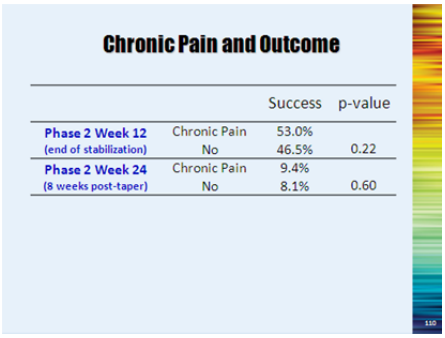
In general, the sociodemographic factors of chronic pain subjects vs. non-chronic pain subjects were very similar. The only factor that differed significantly was age, in which the chronic pain cohort was significantly older (35.4 years) than the non-chronic pain cohort (30.8 years).



Slide 109: Chronic Pain Subjects were…

Chronic pain at baseline was not related to outcomes in either phase 1 or during phase 2 while taking buprenorphine-naloxone; 30 of 379 subjects (7.9%) with chronic pain achieved success in phase 1 compared to 13 of 274 (4.7%) without chronic pain. Seventy-nine of 149 phase 2 subjects (53%) with chronic pain achieved success at week 12 compared with 98 of 211 subjects (46.4%) without chronic pain.

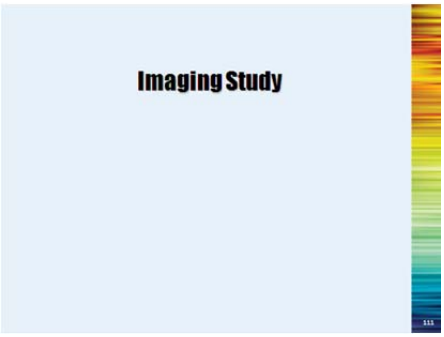
In other words, pain did not determine the results, and was not predictive of outcome.



Slide 110: Chronic Pain and Outcome

Chronic pain subjects were slightly more likely than non-chronic pain subjects to be successful at phase 2, week 12, and at phase 2, week 24. The results were not statistically significant.

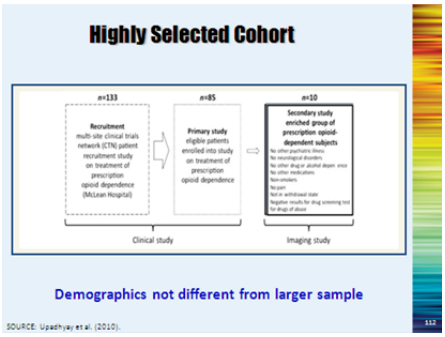
At this point, the presentation will transition to a brief discussion of a small imaging study, and then the implications of POATS will be presented.



Slide 111: Imaging Study

A dramatic increase in the negative consequences associated with prescription drug abuse (e.g., emergency department visits and overdoses) has occurred within the last 10 years. The consequences of long-term prescription opioid use and dependence on the brain are largely unknown, and any speculation is inferred from heroin and methadone studies. Thus, no data have directly demonstrated the effects of prescription opioid use on brain structure and function in humans. To pursue this issue, Upadhyay and colleagues used structural magnetic resonance imaging, diffusion tensor imaging and resting-state functional magnetic resonance imaging in a highly enriched group of prescription opioid-dependent patients [(n= 10); from a larger study on prescription opioid dependent patients (n= 133)] and matched healthy individuals (n= 10) to characterize possible brain alterations that may be caused by long-term prescription opioid use.

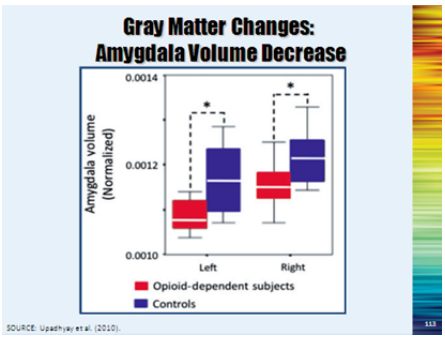
Reference:
Published in 2010 in *Brain* by Upadhyay and colleagues, and led by David Borsook, P.A.I.N. Group, Harvard Medical School & Brain Imaging Center McLean Hospital.



Slide 112: Highly Selected Cohort

Criteria for patient selection included: (1) no dependence on alcohol or other drugs; (2) no comorbid psychiatric or neurological disease; and (3) no medical conditions, including pain.

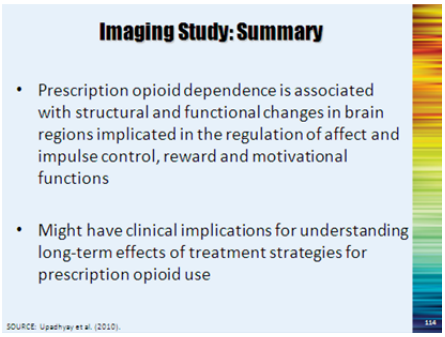
Two animations appear on this slide. Click forward one time to enlarge the information in the third text box; click forward a second time to highlight the note that the demographics of the imaging study sample were similar to the demographics of POATS.



Slide 113: Gray Matter Changes: Amygdala Volume Decrease

In comparison to control subjects, individuals with opioid dependence displayed bilateral volumetric loss in the amygdala. Prescription opioid-dependent subjects had significantly decreased anisotropy in axonal pathways specific to the amygdala (i.e. stria terminalis, ventral amygdalofugal pathway and uncinate fasciculus) as well as the internal and external capsules. In the patient group, significant decreases in functional connectivity were observed for seed regions that included the anterior insula, nucleus accumbens and amygdala subdivisions.

Correlation analyses revealed that longer duration of prescription opioid exposure was associated with greater changes in functional connectivity. Finally, changes in amygdala functional connectivity were observed to have a significant dependence on amygdala volume and white matter anisotropy of efferent and afferent pathways of the amygdala.

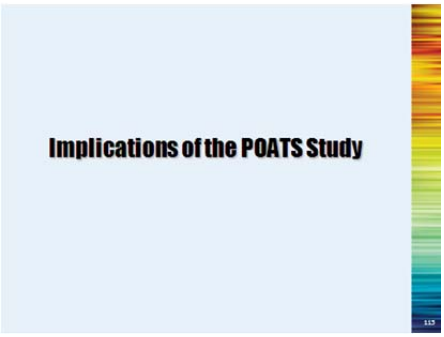


Slide 114: Imaging Study: Summary

The amygdala is considered a key brain system involved in addiction. The significantly smaller amygdala volumes observed have also been reported for cocaine and alcohol dependence. Opioids are known to decrease dendritic spine density, which could explain smaller amygdala volumes.

Decreases in white matter FA observed in a number of pathways, including neuronal circuits involving amygdala, nucleus accumbens and the insula, pathways connecting the amygdala with other cortical and subcortical structures. These amygdala-related alterations may, in part, facilitate vulnerability to risky behaviors. Previous studies have reported on changes in white matter anisotropy in patients with alcohol dependence, chronic marijuana use. The white matter changes observed in present study parallel these previous studies of drug dependence implicates changes in common pathways. The effects of prescription opioid dependence on white matter tract integrity maybe attributed to a direct deleterious effect of opioids on myelin or other axonal membrane properties.

These findings suggest that prescription opioid dependence is associated with structural and functional changes in brain regions implicated in the regulation of affect and impulse control, as well as in reward and motivational functions. These results may have important clinical implications for uncovering the effects of long-term prescription opioid use on brain structure and function.



Slide 115: Implications of the POATS Study
(Transition Slide)

In this multi-site study, the first large randomized controlled trial of patients dependent on prescription opioids, the rate of unsuccessful outcomes after buprenorphine-naloxone taper, even after a 12-week treatment, was high, exceeding 90%. In contrast, subjects with longer stabilization with buprenorphine-naloxone treatment prior to the taper had considerably better opioid use outcomes during treatment than did those who had been tapered off the medication. The addition of individual ODC to buprenorphine-naloxone treatment plus medical management did not improve opioid use outcomes. Relapse rates were comparable for both groups following the taper.

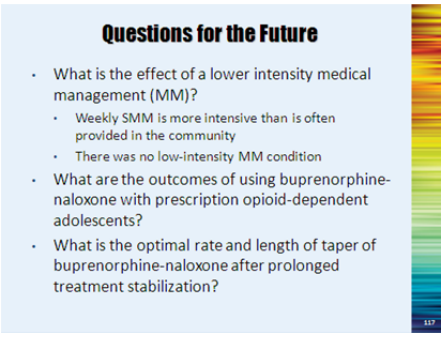
The high rate of unsuccessful outcomes after buprenorphine-naloxone taper is notable in light of the good prognostic characteristics of the population (i.e., largely employed, well educated, relatively brief opioid use histories, and little other current substance use) and previous research suggesting that individuals dependent on prescription opioids might have better outcomes than those dependent on heroin.

Slide 116: Take Home Messages

The POATS results support long-term medication-assisted treatment. Buprenorphine works really well, and long-term treatment is more effective than short-term treatment.

The present study findings suggest that physicians can successfully treat many individuals dependent on prescription opioids, with or without chronic pain, using buprenorphine-naloxone with relatively brief weekly medical management visits.

This study has important implications for clinical practice. The lack of a difference between SMM and SMM+ODC was similar to a finding of Fiellin et al. (2006) with a largely heroin-dependent population, despite the fact that POATS had a greater contrast in intensity of counseling conditions than did the Fiellin study. This supports the national trend toward treatment of opioid dependence by physicians in office-based practice. Furthermore, patients dependent on prescription opioids, with or without chronic pain, are most likely to reduce their opioid use during the first several months of treatment while receiving buprenorphine-naloxone; if tapered off this medication, the likelihood of relapse to opioid use or dropout from treatment is overwhelmingly high.



Slide 117: Questions for the Future

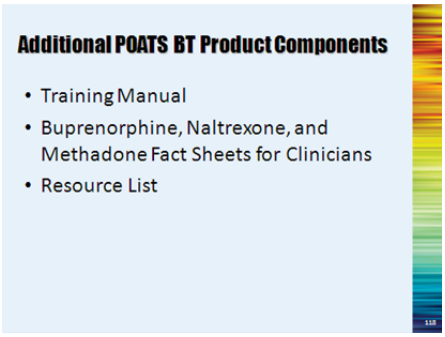
More research is needed to understand the impact of counseling intensity on buprenorphine-naloxone treatment outcomes. Additionally, the fact that there were no differences between groups does not mean that counseling was unimportant or unnecessary. It simply means that increasing intensity did not lead to better results.

Because POATS did not include a condition providing infrequent or no medical management, it is unknown at this time whether providing less intensive medical management, perhaps in conjunction with group counseling, would affect outcomes. This is of particular interest, because not all physicians who treat opioid dependence with buprenorphine see patients as often as weekly.

Conversely, more frequent individual counseling, such as that provided in an intensive outpatient program, might have produced better outcomes than did SMM+ODC.

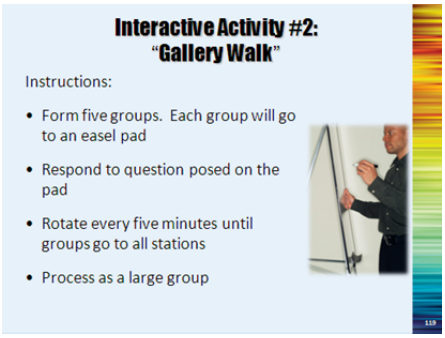
Additionally, more research is needed to understand how the POATS results relate to adolescents and the optimal length of buprenorphine-naloxone taper following prolonged treatment stabilization.

From *Addiction Professional* article (11/14/11): "…The finding on counseling is likely to gain the most attention in the [SUD] treatment field, particularly given that the advent of advanced medication treatments for addiction has come with the proviso that medications are the most effective when used in conjunction with counseling." While the researchers acknowledge that the research team expected better results from higher intensity counseling in this study (SMM+ODC), they warn against any blanket conclusions drawn from this outcome.



Slide 118: Additional POATS BT Product Components

This list includes additional POATS BT product components. All POATS BT products are available for viewing and downloading in the *NIDA/SAMSHA Blending Initiative* section of the ATTC Network website, http://www.attcnetwork.org or the NIDA Blending website, http://www.nida.nih/gov/blending/.



Slide 119: Interactive Activity #2: "Gallery Walk"

ACTIVITY – 30 to 35 minutes

Preparation prior to the training is needed for this activity.

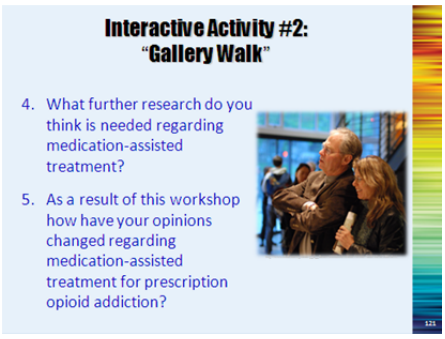
Prior to the exercise, tape an easel pad sheet at each of five stations around the room, each with a question written on the top of the sheet. Be sure to spread them around the room so that no two stations are too close together. Use the five questions listed on slides 120-121.

Among the participants, form five groups and assign each group to one of the stations. Give each group about 5 minutes to brainstorm and respond to the question and write responses on the chart paper, then ask each group to rotate clockwise to the next station. Let them know that you expect there to be overlap with regards to responses. Continue the process until each group arrives back to where they started.

Slide 120: Interactive Activity #2: "Gallery Walk"

The following are the first three questions:

- ***Before today, what were your thoughts about medication-assisted treatment?***
- ***What challenges do you see regarding the provision of medication-assisted treatment for those addicted to prescription opioids?***
- ***What are the advantages of medication-assisted treatment for prescription opioid addiction?***



Slide 121: Interactive Activity #2: "Gallery Walk"

The following are the final two questions:

- ***What further research do you think is needed regarding medication-assisted treatment?***
- ***As a result of this workshop, how (if any) have your opinions changed regarding medication-assisted treatment for prescription opioid addiction?***

When all groups have contributed to all five questions, ask them to rotate one more time to the station where they started. Ask each group to read what was added to their original responses. Then process the exercise by asking a spokesperson for each group to summarize the answers at each respective station.

Slide 122: Final Slide

Field any final questions and thank participants for attending the POATS training. For additional information, refer participants to the ATTC Network website: http://www.attcnetwork.org, or to the NIDA Blending website: http://www.nida.nih.gov/blending/.