

Module III

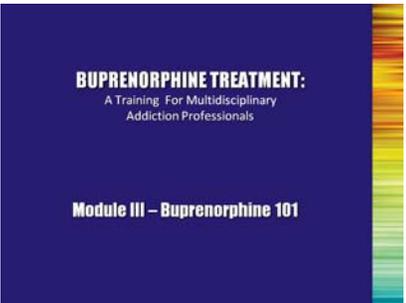
Buprenorphine 101



Module III: Buprenorphine 101

This module is designed to provide an overview of the development and pharmacology of buprenorphine. It also provides, in summary form, information about treatment using the medication: induction, maintenance, and medically-assisted withdrawal. The primary focus of the treatment section is to provide an overview of the medical aspects of treatment and the role of non-medical practitioners at each of these phases of treatment. Specific information on counseling patients who are taking buprenorphine is provided in Module VI.

To avoid training participants perceiving the trainer(s) as “selling” buprenorphine, be sure to frame the availability of buprenorphine as an additional option (not just a replacement for/alternative to methadone). The availability of buprenorphine for the treatment of opioid addiction is allowing for an expansion of opioid treatment. The training is not, in any way, meant to advocate one treatment over another; instead, it is an addition to the repertoire of medications available for the treatment of opioid addiction.

 <p>BUPRENORPHINE TREATMENT: A Training For Multidisciplinary Addiction Professionals</p> <p>Module III – Buprenorphine 101</p>	<p>Slide 1: Title Slide</p> <p>Now it’s time to talk specifically about buprenorphine. What is this medication and how does it work? That is the question that we will answer in this module.</p>	<p>Slide 1</p>
 <p>Goals for Module III</p> <p>This module reviews the following:</p> <ul style="list-style-type: none"> • The development of buprenorphine • The differences between the combination (buprenorphine/naloxone) and the mono (buprenorphine only) tablets • Use of buprenorphine in opioid treatment <ul style="list-style-type: none"> – Induction – Maintenance – Medically-Assisted Withdrawal 	<p>Slide 2: Goals for Module III</p> <p>Now that we have reviewed the basics of opioid addiction and treatment, we will now review:</p> <ul style="list-style-type: none"> • The development of buprenorphine • Compare the differences between the combination (buprenorphine/naloxone) and the mono (buprenorphine only) tablets available for the treatment of opioid addiction • Examine the use of buprenorphine in the various phases of opioid treatment (e.g., induction, maintenance, medically-assisted withdrawal). 	<p>Slide 2</p>

Development of Tablet Formulations of Buprenorphine

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



Subutex® (buprenorphine) Suboxone® (buprenorphine/naloxone)

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

Slide 3: Development of Tablet Formulations for Buprenorphine

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

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

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

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

These medications have a tremendous amount of research behind them to show that they are both safe and effective in the treatment of opioid addiction.

Buprenorphine: A Science-Based Treatment

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

- Placebo (Johnson et al., 1995; Kakko et al., 2003; Ling et al., 1998)
- Methadone (Fischer et al., 1999; Johnson, Jaffe, & Fudala, 1992; Schottenfeld et al., 1997; Strain et al., 1994)
- Methadone and LAAM (levo-alpha-acetyl-methadol) (Johnson et al., 2008)

Slide 4: 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.

References:

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

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

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

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

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

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

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

Slide 4



Moving Science-Based Treatments into Clinical Practice

- A challenge in the addiction field is moving science-based treatment methods into clinical settings.
- NIDA and CSAT initiatives are underway to bring research and clinical practice closer.
- Buprenorphine treatment represents an achievement in this effort.

Slide 5: Moving Science-Based Treatments into Clinical Practice

Many treatments that are developed never make it into real-world practice.

This has been a problem for quite some time and both the National Institute on Drug Abuse (NIDA) and the Substance Abuse Mental Health Services Administration (SAMHSA) has recognized this. The Blending Team that developed these materials resulted from one initiative designed to help move scientific findings into practical application: The NIDA/SAMHSA Blending Initiative.

Buprenorphine is an important treatment advancement and represents an exciting opportunity for individuals to develop strategies to work with both providers and researchers to find ways to make this treatment a readily-available option.

Slide 5

Buprenorphine Research Outcomes

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

Slide 6: 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).

However, it is unclear if buprenorphine can be as effective as higher doses of methadone (such as 80 mg per day to more than 100 mg per day).

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).

Note to the Trainer(s): LAAM is no longer being marketed in the US due to safety concerns. This information is provided as evidence of efficacy of buprenorphine.

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

Bullet #4: When compared to placebo-plus-counseling, 3/4 of the patients receiving buprenorphine and counseling were still in treatment after one year. None of the placebo patients were retained.

References: Bullet #1

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

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

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

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

Reference: Bullet #2

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

Slide 6



	<p>Slide 6: Buprenorphine Research Outcomes, continued</p> <p><u>Reference: Bullet #3</u></p> <p>Ling, W., Charuvastra, C., Collins, J. F., Batki, S., Brown, L. S., Jr., Kintaudi, P., ... Segal, D. (1998). Buprenorphine maintenance treatment of opiate dependence: A multicenter, randomized clinical trial. <i>Addiction</i>, 93, 475–486.</p> <p><u>Reference: Bullet #4</u></p> <p>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. <i>The Lancet</i>, 361(9358), 662-668.</p>	<p>Slide 6</p> 
 <p>Buprenorphine as a Treatment for Opioid Addiction</p> <ul style="list-style-type: none"> • A synthetic opioid • Described as a mixed opioid agonist-antagonist (or partial agonist) • Available for use by certified physicians outside traditionally licensed opioid treatment programs 	<p>Slide 7: Buprenorphine as a Treatment for Opioid Addiction</p> <p>Buprenorphine is a partial agonist, resulting in a good safety profile for the medication.</p> <p>With the changes in the treatment legislation, this medication becomes the first available outside of the opioid treatment program (OTP) system. This expands both the availability of and access to treatment.</p>	<p>Slide 7</p>

The Role of Buprenorphine in Opioid Treatment

- Partial Opioid Agonist
 - Produces a ceiling effect at higher doses
 - Has effects of typical opioid agonists—these effects are dose dependent up to a limit
 - Binds strongly to opiate receptor and is long-acting
- Safe and effective therapy for opioid maintenance and detoxification

Slide 8: The Role of Buprenorphine in Opioid Treatment

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

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

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

This high affinity for and slow dissociation from the receptor result in buprenorphine blocking the effects of other opioids, such as heroin. Additionally, the high affinity and slow dissociation give rise to buprenorphine’s prolonged therapeutic effects.

Clinical trials have demonstrated that buprenorphine is a safe and effective medication for both opioid maintenance and medically-assisted withdrawal (detoxification). Additionally, because buprenorphine is very long-acting, dosing can occur on a less-than-daily basis, as infrequently as three times per week.

Slide 8

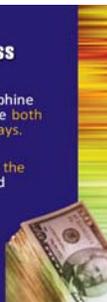
 <p>Advantages of Buprenorphine in the Treatment of Opioid Addiction</p> <ol style="list-style-type: none"> 1. Patient can participate fully in treatment activities and other activities of daily living easing their transition into the treatment environment 2. Limited potential for overdose (Johnson et al., 2003) 3. Minimal subjective effects (e.g., sedation) following a dose 4. Available for use in an office setting 5. Lower level of physical dependence 	<p>Slide 9: Advantages of Buprenorphine in the Treatment of Opioid Addiction</p> <p>When transitioned onto buprenorphine, patients can participate fully in treatment activities rather than being sick from withdrawal for several days. This means that treatment can begin as soon as they seek it (while motivation is high).</p> <p>There are no known cases of overdose directly related to buprenorphine. To date, cases in which overdose has occurred involved use of alcohol or other respiratory depressants (e.g., benzodiazepines). Refer to Johnson, et al. 2003, for a more detailed discussion.</p> <p>Patients report minimal sedation following a dose.</p> <p>The treatment setting can be determined to fit the needs of the patient - outpatient treatment or office-based.</p> <p><u>Reference:</u></p> <p>Johnson, R. E., Strain, E. C., & Amass, L. (2003). Buprenorphine: How to use it right. <i>Drug and Alcohol Dependence</i>, 70, S59-S77.</p>	<p>Slide 9</p> 
 <p>Advantages of Buprenorphine/Naloxone</p> <ul style="list-style-type: none"> • Discourages IV use • Diminishes diversion 	<p>Slide 10: Advantages of Buprenorphine/Naloxone</p> <p>The buprenorphine/naloxone formulation has some advantages compared with the buprenorphine only formulation:</p> <ul style="list-style-type: none"> • It discourages injection of the product because, when injected, the naloxone will lead to withdrawal, whereas when taken sublingually as prescribed, it will not have that effect. • Because of the above point, the combination tablet lowers the likelihood that the medication will be diverted. • An additional advantage to the buprenorphine/naloxone formulation is it allows for take-home dosing. 	<p>Slide 10</p>

<p>Disadvantages of Buprenorphine in the Treatment of Opioid Addiction</p> <ol style="list-style-type: none"> 1. Greater medication cost 2. Lower level of physical dependence (i.e., patients can discontinue treatment) 3. Detectable only in specific urine toxicology screenings 	<p>Slide 11: Disadvantages of Buprenorphine in the Treatment of Opioid Addiction</p> <p>There are definitely disadvantages to the medication, as well.</p> <p>Buprenorphine is more costly than methadone. According to the manufacturer, Suboxone® (16 mg/day) costs \$308 for a month's supply, compared to less than \$30 for a month's supply of methadone at usual doses.</p> <p>Overall, the medication causes a lower level of physical dependence. While this is generally seen as an advantage of the medication, it does make it easier for patients to discontinue treatment and return to use.</p> <p>Buprenorphine is detectable in urine tests however many tests do not include buprenorphine in the panel of drugs screened. Special tests may need to be ordered to ensure that compliance with the medication can be monitored.</p>	<p>Slide 11</p>
<p>Use of Buprenorphine: Studies on Cost-Effectiveness</p> <ul style="list-style-type: none"> • Medication costs are only one factor. Costs of providing treatment also include costs associated with clinic visits, staff time, etc. These costs are greater for methadone. • While not yet studied in young adults, research on adult populations has demonstrated cost effectiveness of buprenorphine across several indicators. 	<p>Slide 12: Use of Buprenorphine: Studies on Cost-Effectiveness</p> <p>There has been much discussion regarding the costs associated with the use of buprenorphine for the treatment of opioid dependence. When considering the costs of providing treatment, you must also include costs associated with clinic visits, staff time, and general operating and facility expenditures.</p> <p>Recently, research conducted on adult populations has demonstrated the utilization of buprenorphine is cost-effective across several indicators.</p>	<p>Slide 12</p>

Use of Buprenorphine: Studies on Cost-Effectiveness

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

(Doran et al., 2003)



Slide 13: Use of Buprenorphine: Studies on Cost-Effectiveness

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

Key findings included:

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

Reference:

Doran, C. M., Shanahan, M., Mattick, R. P., Bell, J., White, J., & Ali, R. (2003). Buprenorphine versus methadone maintenance: A cost effectiveness analysis. *Drug and Alcohol Dependence*, 71(3), 295-302.

Slide 13



<p>Use of Buprenorphine: Studies on Cost-Effectiveness, cont'</p> <ul style="list-style-type: none"> • Treatment with buprenorphine-naloxone was associated with a reduction in opioid utilization and cost in the first year of follow-up (Kaur & McQueen, 2008). • Systematic review found good studies supporting buprenorphine as a cost effective approach to opioid treatment (Doran, 2008). 	<p>Slide 14: Use of Buprenorphine: Studies on Cost-Effectiveness, cont'</p> <p>Another study, conducted by Kaur and McQueen (2008), found that the treatment with buprenorphine/naloxone was associated with a reduction in opioid utilization and cost in the first year of follow-up.</p> <p>Doran (2008) conducted a systematic review of the literature and found a number of studies supporting buprenorphine as a cost-effective approach to opioid treatment.</p> <p><u>References:</u></p> <p>Doran, C. M. (2008). Economic evaluation of interventions to treat opiate dependence: a review of the evidence. <i>Pharmacoeconomics</i>, 26(5), 371-393.</p> <p>Kaur, A. D., McQueen, A. & Jan, S. (2008). Opioid drug utilization and cost outcomes associated with the use of buprenorphine-naloxone in patients with a history of prescription opioid use. <i>Journal of Managed Care Pharmacy</i>, 14(2), 186-194.</p>	<p>Slide 14</p> 
<p>Use of Buprenorphine: Studies on Cost-Effectiveness, cont'</p> <ul style="list-style-type: none"> • Another study in Australia found buprenorphine demonstrated lower crime costs and higher quality adjusted life years (QALY), concluding the likelihood of net benefits from substituting buprenorphine for methadone. <p><small>(Harris, Gospodarevskaya, & Ritter, 2005)</small></p> 	<p>Slide 15: Use of Buprenorphine: Studies on Cost-Effectiveness, cont'</p> <p>Harris and colleagues (2005) were the first to examine the cost-effectiveness of buprenorphine as maintenance treatment for heroin dependence in a primary care setting. The study was a randomized, open-label, 12-month trial of 139 heroin-dependent patients in a community setting receiving individualized treatment regimens of buprenorphine or methadone. The study took a broad societal perspective and included health, crime and personal costs. The main outcomes were incremental cost per additional day free of heroin use and per the quality adjusted life years (QALY).</p> <p>The researchers found that buprenorphine demonstrated lower crime costs and higher QALY.</p> <p><u>Reference:</u></p> <p>Harris, A. H., Gospodarevskaya, E., & Ritter, A. J. (2005). A randomised trial of the cost effectiveness of buprenorphine as an alternative to methadone maintenance treatment for heroin dependence in a primary care setting. <i>Pharmacoeconomics</i>, 23(1), 77-91.</p>	<p>Slide 15</p> 

<p>Why was Buprenorphine/Naloxone Combination Developed?</p> <ul style="list-style-type: none"> • Developed in response to increased reports of buprenorphine abuse outside of the U.S. • The combination tablet is specifically designed to decrease buprenorphine abuse by injection, especially by out of treatment opioid users. 	<p>Slide 16: Why was Buprenorphine/Naloxone Combination Developed?</p> <p>In other countries where buprenorphine has been available, there were reports of increasing abuse of the medication. Therefore, the U.S. developers worked to find a way of preventing misuse of the medication as much as possible.</p> <p>Since use of the buprenorphine/naloxone combination tablet by injection will cause withdrawal, the likelihood of misuse by out-of-treatment opioid users is greatly decreased.</p>	<p>Slide 16</p>
<p>What is the Ratio of Buprenorphine to Naloxone in the Combination Tablet?</p> <ul style="list-style-type: none"> • Each tablet contains buprenorphine and naloxone in a 4:1 ratio <ul style="list-style-type: none"> – Each 8 mg tablet contains 2 mg of naloxone – Each 2 mg tablet contains 0.5 mg of naloxone • Ratio was deemed optimal in clinical studies <ul style="list-style-type: none"> – Preserves buprenorphine's therapeutic effects when taken as intended sublingually – Sufficient dysphoric effects occur if injected by some physically dependent persons to discourage abuse 	<p>Slide 17: What is the Ratio of Buprenorphine to Naloxone in the Combination Tablet?</p> <p>The combination includes buprenorphine and naloxone in a ratio of 4:1.</p> <p>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).</p>	<p>Slide 17</p>

Why Combining Buprenorphine and Naloxone Sublingually Works

- Buprenorphine and naloxone have different sublingual (SL) to injection potency profiles that are optimal for use in a combination product.

SL Bioavailability

Buprenorphine 40-60%

Naloxone 10% or less

Potency

Buprenorphine = 2:1

Naloxone = 15:1

(Chiang & Hawks, 2003)

Slide 18: Why Combining Buprenorphine and Naloxone Sublingually Works

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

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

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

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

Reference:

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

Slide 18



Buprenorphine/Naloxone: What You Need to Know

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

Slide 19: Buprenorphine/Naloxone: What You Need to Know

- The effect of the combination tablet is virtually identical to the buprenorphine-only product when taken sublingually.
- Both formulations demonstrate the ceiling effect at higher doses.
- Both formulations prevent the intoxicating effects if someone decides to also use another opioid.
- They are long-acting because of the high receptor affinity; meaning they bind strongly to the receptor site.

Additional Information for the Trainer:

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 to 32 mg dose range for sublingual tablets. Higher doses are unlikely to produce greater effects.

Note to the Trainer(s): At 16 mg, 96% of the receptor sites are full; at 24 mg, approximately 99% of the receptor sites are full.

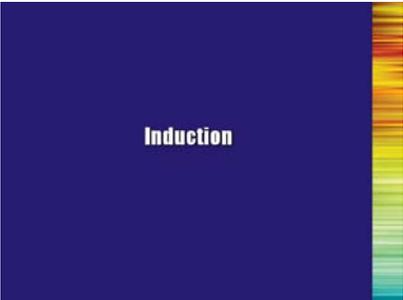
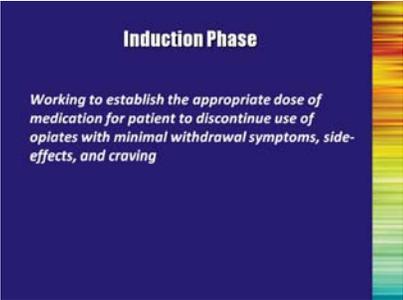
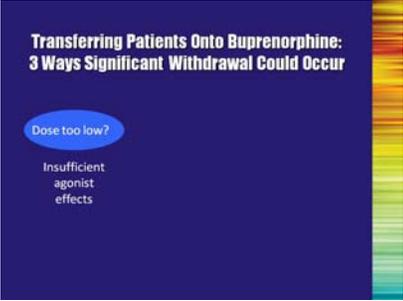
Respiratory depression from buprenorphine (or buprenorphine/ naloxone) overdose is less likely than from other opioids. There is no evidence of organ damage with chronic use of buprenorphine, but increases in liver enzymes are sometimes seen. There is no evidence of significant disruption of cognitive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

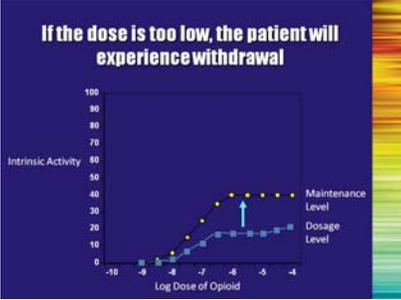
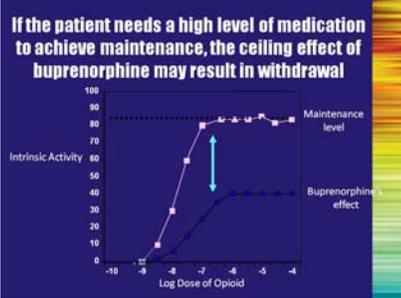
Side Effects

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

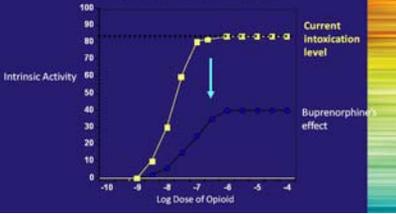
Slide 19



 <p>The Use of Buprenorphine in the Treatment of Opioid Addiction</p> <p>Induction Maintenance Tapering Off/Medically-Assisted Withdrawal</p>	<p>Slide 20: The Use of Buprenorphine in the Treatment of Opioid Addiction (Induction, Maintenance, Tapering Off/Medically-assisted Withdrawal) (Transition Slide)</p> <p>Now let’s look at how people are transitioned onto buprenorphine and then examine the two primary treatment options: maintenance and medically-assisted withdrawal.</p>	<p>Slide 20</p>
 <p>Induction</p>	<p>Slide 21: Induction</p> <p>The term <u>induction</u> refers to the procedures used to transition someone from other opioids onto buprenorphine.</p>	<p>Slide 21</p>
 <p>Induction Phase</p> <p><i>Working to establish the appropriate dose of medication for patient to discontinue use of opiates with minimal withdrawal symptoms, side-effects, and craving</i></p>	<p>Slide 22: Induction Phase</p> <p>During induction, the physician works with the patient to figure out the most effective dose so that he/she can stop other opioid use with minimal withdrawal symptoms.</p> <p>While the physician primarily guides this process, the multidisciplinary team is critical in providing supportive care and counseling to help the patient through the process.</p>	<p>Slide 22</p>
 <p>Transferring Patients Onto Buprenorphine: 3 Ways Significant Withdrawal Could Occur</p> <p>Dose too low? Insufficient agonist effects</p>	<p>Slide 23: Transferring Patients Onto Buprenorphine: 3 Ways Significant Withdrawal Could Occur</p> <p>There are three ways that a patient can experience withdrawal symptoms.</p> <p>First, if an insufficient dose of buprenorphine is given, the person may experience withdrawal from being undermedicated.</p>	<p>Slide 23</p>

 <p>If the dose is too low, the patient will experience withdrawal</p>	<p>Slide 24: If the dose is too low, the patient will experience withdrawal</p> <p>This graph represents how under-medication can result in withdrawal symptoms. If the patient is given a low level of medication (represented by the green line), but needs a higher level in order to not feel sick (represented by the white line), the person will feel sick unless the dosage is increased to bring them up to this level.</p>	<p>Slide 24</p>
 <p>Transferring Patients Onto Buprenorphine: 3 Ways Significant Withdrawal Could Occur</p> <ul style="list-style-type: none"> Dose too low? <ul style="list-style-type: none"> Insufficient agonist effects Not full agonist <ul style="list-style-type: none"> May not fully replace 	<p>Slide 25: Transferring Patients Onto Buprenorphine: 3 Ways Significant Withdrawal Could Occur</p> <p>A second way that a person can experience withdrawal has to do with the properties of buprenorphine itself—the ceiling effect.</p>	<p>Slide 25</p>
 <p>If the patient needs a high level of medication to achieve maintenance, the ceiling effect of buprenorphine may result in withdrawal</p>	<p>Slide 26: If the patient needs a high level of medication to achieve maintenance, the ceiling effect of buprenorphine may result in withdrawal</p> <p>As described before, as the dose of buprenorphine increases, the agonist effects level off. For someone who is dependent on very high doses of opioids, they may need an effect greater than can be achieved with buprenorphine in order to not feel sick.</p> <p>In this case, treatment would need to be provided using a full agonist (e.g. methadone) or the person would need to taper down their level of drug use to a lower level before switching to buprenorphine. This can be done in a structured OTP, but should not be attempted with someone using illicit opioids.</p>	<p>Slide 26</p>
 <p>Transferring Patients Onto Buprenorphine: 3 Ways Significant Withdrawal Could Occur</p> <ul style="list-style-type: none"> Dose too low? <ul style="list-style-type: none"> Insufficient agonist effects Not full agonist <ul style="list-style-type: none"> May not fully replace Precipitates Withdrawal <ul style="list-style-type: none"> Ceiling effect 	<p>Slide 27: Transferring Patients Onto Buprenorphine: 3 Ways Significant Withdrawal Could Occur</p> <p>Finally, there is precipitated withdrawal. This also has to do with the ceiling effect and receptor affinity.</p>	<p>Slide 27</p>

Buprenorphine will replace other opioids at the receptor site; therefore the patient experiences withdrawal.



Slide 28: Buprenorphine will replace other opioids at the receptor site; therefore the patient experiences withdrawal

Slide 28

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

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

Direct Buprenorphine Induction from Short-Acting Opioids

- Ask patient to abstain from short-acting opioid (e.g., heroin) for at least 6 hrs. and be in mild withdrawal before administering buprenorphine/naloxone.
- When transferring from a short-acting opioid, be sure the patient provides a methadone-negative urine screen before 1st buprenorphine dose.

(Annon et al., 2004; Johnson et al., 2003)

Slide 29: Direct Buprenorphine Induction from Short-Acting Opioids

Slide 29

Patients who are using either short- or long-acting opioids can be inducted onto buprenorphine/naloxone. The PHYSICIAN is responsible for this aspect of the patient's care.

The multidisciplinary addiction professional should be available, however, during the induction process to provide supportive counseling.

In order to be inducted onto buprenorphine, the patient must be in mild withdrawal. This ensures that they have a smooth transition onto the medication and will not have unexpected withdrawal symptoms.

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

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

Slide 29: Direct Buprenorphine Induction from Short-Acting Opioids, Continued

As previously discussed, if a patient transitions immediately from heroin to buprenorphine, buprenorphine will replace the heroin at the receptor and the patient will have the experience of suddenly having much less opioids in their system than they are used to – they will go into withdrawal. However, if they are already in mild withdrawal, the buprenorphine will have the expected agonist effects and the patient will experience a comfortable transition.

The patient should also be monitored for methadone use, as this can complicate the transition as well.

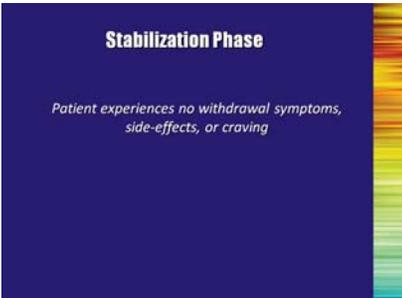
Reference:

Amass, L., Ling, W., Freese, T. E., Reiber, C., Annon J. J., Cohen, A. J., ... Horton, T. (2004). Bringing buprenorphine-naloxone detoxification to community treatment providers: The NIDA Clinical Trials Network field experience. *American Journal on Addictions, 13*(Suppl1), S42-S66.

Johnson, R. E., Strain, E. C., & Amass, L. (2003). Buprenorphine: How to use it right. *Drug and Alcohol Dependence, 70*, S59-S77.

Wesson, D. R., & Ling, W. (2003). The Clinical Opiate Withdrawal Scale (COWS). *Journal of Psychoactive Drugs, 35*, 253-259.



 <p>Direct Buprenorphine Induction from Long-Acting Opioids</p> <ul style="list-style-type: none"> Clinical experience has suggest that induction procedures with patients receiving long-acting opioids (e.g. methadone-maintenance patients) are basically the same as those used with patients taking short-acting opioids, except: <ul style="list-style-type: none"> The time interval between the last dose of medication and the first dose of buprenorphine must be increased. At least 24 hrs should elapse before starting buprenorphine and longer time periods may be needed (up to 48 hrs). Urine drug screening should indicate no other illicit opiate use at the time of induction. <small>(Center for Substance Abuse Treatment, 2004)</small>	<p>Slide 30: Direct Buprenorphine Induction from Long-Acting Opioids</p> <p>Clinical experience has indicated that patients being transitioned from long-acting opioids (e.g., methadone) can be successfully inducted using similar procedures as those used for short-acting opioids</p> <p>According to SAMHSA's <i>Clinical Guidelines for the Use of Buprenorphine in the Treatment of Opioid Addiction (TIP 40)</i>, patients should be tapered to a lower dose of their current medication (e.g., 30 mg or less of methadone). The patient should not begin receiving buprenorphine until at least 24 hours after their last dose and then can begin on buprenorphine. These patients should begin on a very low dose of buprenorphine (e.g., 2 mg) and then gradually receive more if needed.</p> <p><u>Reference:</u></p> <p>Center for Substance Abuse Treatment. (2004). <i>Clinical Guidelines for the Use of Buprenorphine in the Treatment of Opioid Addiction</i>. Treatment Improvement Protocol (TIP) Series 40. DHHS Publication No. (SMA) 04-3939. Rockville, MD: Substance Abuse and Mental Health Services Administration.</p>	<p>Slide 30</p> 
 <p>Stabilization and Maintenance</p>	<p>Slide 31: Stabilization and Maintenance (Transition Slide)</p> <p>Once the patient is on the medication, the next step is to make sure he/she is <u>stabilized</u>.</p>	<p>Slide 31</p>
 <p>Stabilization Phase</p> <p><i>Patient experiences no withdrawal symptoms, side-effects, or craving</i></p>	<p>Slide 32: Stabilization Phase</p> <p>By stabilization, we mean that they do not experience any negative symptoms or craving.</p> <p>At this point, the decision can be made to either move on to the maintenance phase or to withdraw with medically-assisted withdrawal.</p>	<p>Slide 32</p>

<p>Maintenance Phase</p> <p>Goals of Maintenance Phase: Help the patient stop and stay away from illicit drug use and problematic use of alcohol</p> <ol style="list-style-type: none"> 1. Continue to monitor cravings to prevent relapse 2. Address psychosocial and family issues 	<p>Slide 33: Maintenance Phase</p> <p>The goal of maintenance is cessation of illicit drug use and problematic alcohol use.</p> <p>The treatment professional should address any underlying issues, such as psychiatric co-morbidity and psychosocial issues (employment, legal, family/social, etc.).</p>	<p>Slide 33</p>
<p>Maintenance Phase</p> <p>Psychosocial and family issues to be addressed:</p> <ol style="list-style-type: none"> a) Psychiatric co-morbidity b) Family and support issues c) Time management d) Employment/financial issues e) Pro-social activities f) Legal issues g) Secondary drug/alcohol use 	<p>Slide 34: Maintenance Phase</p> <p>During maintenance treatment, providers should assess the patient and provide treatment for other issues that the patient is facing, to help get him/her stabilized and live a more fulfilled life.</p> <p><i>Read/summarize the bullet points.</i></p> <p>Maintenance treatment may be fairly short (e.g., <12 months) or a lifetime process. Research and clinical consensus (CSAT, 2004) suggest that the longer a patient is maintained on medication treatment (methadone or buprenorphine), the higher the likelihood that they will experience less illicit drug use and the fewer complications.</p> <p><u>Reference:</u></p> <p>Center for Substance Abuse Treatment. (2004). <i>Clinical Guidelines for the Use of Buprenorphine in the Treatment of Opioid Addiction</i>. Treatment Improvement Protocol (TIP) Series 40. DHHS Publication No. (SMA) 04-3939. Rockville, MD: Substance Abuse and Mental Health Services Administration.</p>	<p>Slide 34</p>  

 <p>Buprenorphine Maintenance: Summary</p> <ul style="list-style-type: none"> • Take-home dosing is safe and preferred by patients, but patient adherence will vary and this can impact treatment outcomes. • 3x/week dosing with buprenorphine/naloxone is safe and effective as well (Hansen et al., 2012). • <i>Counseling needs to be integrated into any buprenorphine treatment plan.</i> 	<p>Slide 35: Buprenorphine Maintenance: Summary</p> <p>Use of take-home dosing is desired by many patients, but ongoing monitoring is critical to determine compliance.</p> <p>In adults, dosing every day is not necessary. Researchers have demonstrated that a three-time-per-week dosing schedule was safe and effective. Information about less than daily dosing is not available for adolescents.</p> <p>In order to be effective, it is imperative that counseling be incorporated into the treatment plan and supported by the entire multidisciplinary team.</p> <p><u>Reference:</u></p> <p>Amass, L., Kamien, J. B., & Mukulich, S. K. (2001). Thrice weekly supervised dosing with the combination buprenorphine-naloxone tablet is preferred to daily supervised dosing by opioid-dependent humans. <i>Drug and Alcohol Dependence</i>, 61(1), 173-181.</p>	<p>Slide 35</p> 
 <p>Medically-Assisted Withdrawal (a.k.a. Dose Tapering; a.k.a. Detoxification)</p>	<p>Slide 36: Medically-assisted Withdrawal (a.k.a. Dose Tapering; a.k.a. Detoxification) (Transition Slide)</p> <p>Not all patients are appropriate for withdrawal from the medications. Unstable living situations, multiple relapses, previous failed detoxification attempts, or lack of desire to withdraw from opioids, may indicate that maintenance is a better treatment option.</p> <p>Note to the Trainer(s): <i>The following is a very brief summary of medically-assisted withdrawal. For a more in-depth training, insert the Optional Module entitled, Short Term Opioid Withdrawal Using Buprenorphine</i></p>	<p>Slide 36</p> 

<p>Buprenorphine Withdrawal</p> <ul style="list-style-type: none"> • Working to provide a smooth transition from a physically-dependent to non-dependent state, with medical supervision • Medically supervised withdrawal (detoxification) is accompanied with and followed by psychosocial treatment, and sometimes medication treatment (i.e., naltrexone) to minimize risk of relapse. • Medically- supervised withdrawal may lead to early treatment engagement <small>(Brigham et al., 2007)</small> 	<p>Slide 37: Buprenorphine Withdrawal</p> <p>However, if appropriate, the goal of medically-assisted withdrawal is to help patients transition off of opioids so that they are no longer physically dependent.</p> <p>Psychosocial treatment is a critical component of this (and all treatments) to help them avoid relapse and facilitate early engagement in treatment.</p> <p><u>Reference:</u></p> <p>Brigham, G. S., Amass, L., Winhusen, T., Harrer, J. M., & Pelt. A. (2007). Using buprenorphine short-term taper to facilitate early engagement. <i>Journal of Substance Abuse Treatment</i>, 32, 349-356.</p>	<p>Slide 37</p> 
<p>Medically-Assisted Withdrawal (Detoxification)</p> <ul style="list-style-type: none"> • Outpatient and inpatient withdrawal are both possible • How is it done? <ul style="list-style-type: none"> – Switch to longer-acting opioid (e.g., buprenorphine) <ul style="list-style-type: none"> • Taper off over a period of time (a few days to weeks depending upon the program) • Use other medications to treat withdrawal symptoms – Use clonidine and other non-narcotic medications to manage symptoms during withdrawal 	<p>Slide 38: Medically-Assisted Withdrawal (Detoxification)</p> <p>Medically-assisted withdrawal can be successful in either inpatient or outpatient settings. It is important for the multidisciplinary team to provide supportive wrap-around services to get the patient through this difficult stage.</p> <p>This is done by transitioning the patient onto a long-acting opioid like buprenorphine and then tapering him/her off over a period of time.</p> <p>Other medications may be helpful if withdrawal symptoms are present to help the patient to stay comfortable.</p>	<p>Slide 38</p>
<p>Module III – Summary</p> <ul style="list-style-type: none"> • Buprenorphine is available. • Buprenorphine has been proven to be safe and effective in the treatment of opioid addiction. • The multidisciplinary team is critical in buprenorphine treatment. Providing psychosocial and supportive treatment to buprenorphine patients maximizes the potential for success. 	<p>Slide 39: Module III – Summary</p> <p><i>Read/summarize the bullet points.</i></p> <ul style="list-style-type: none"> • Buprenorphine is available. • Buprenorphine has been proven to be safe and effective in the treatment of opioid addiction. • The multidisciplinary team is critical in buprenorphine treatment. Providing psychosocial and supportive treatment to buprenorphine patients maximizes the potential for success. 	<p>Slide 39</p> 