BUPRENORPHINE TRAINING ACTIVITY V5.0 FOR PHYSICIANS PROGRAM SUMMARY / KEY POINTS

ABOUT PRESCRIBING BUPRENORPHINE

- Buprenorphine is a partial agonist opioid used in the treatment of opioid addiction.
- A patient-centered approach to prescribing buprenorphine is important to keep patients fully engaged and empowered in their own recovery
- As a Schedule III drug, buprenorphine has potential for abuse, so a thorough understanding of how to prescribe it effectively and safely is important.
- The Drug Addiction Treatment Act (DATA 2000) and the Comprehensive Addiction and Recovery Act (CARA 2016), amendments to the Controlled Substances Act, makes it possible for qualified physicians, nurse practitioners, and physician assistants to prescribe buprenorphine for opioid detoxification and maintenance therapy in their offices.
- These laws require that the provider must:
    - Be licensed in the state
    - Have a valid DEA registration and identification number for controlled substances and obtain an identification number signifying the waiver (which begins with the prefix X)
    - Comply with federal and state regulations for controlled substances
    - Hold a current waiver
- DATA 2000 requires of physicians an 8-hour training or equivalent and CARA 2016 requires a 24-hour training for nurse practitioners and physician assistants before applying for a waiver to prescribe buprenorphine.
- Providers who qualify and have completed the training apply for their waiver through the Center for Substance Abuse Treatment (CSAT), a division of SAMHSA, which also provides many resources related to prescribing buprenorphine.

IMPACT OF OPIOID USE DISORDER

Prevalence of Opioid Use Disorder and Other Misuse

- About 14% of the population have misused prescription opioids in their lifetimes. At least 2 million people have opioid use disorder.
- Both heroin use and prescription opioid misuse increased in recent years. Oxycodone and hydrocodone are the most commonly misused prescription opioids.

Availability of Treatment for Opioid Use Disorder

- Only a small number of patients who have opioid use disorder or abuse opioids receive the treatment they need.
- About twice as many patients are now maintained on buprenorphine compared to methadone.

Morbidity and Mortality Associated with Opioid Misuse and Opioid Use Disorder

- Prescription opioids are a factor in around five times more ER cases than heroin.
- Heroin and prescription opioids rank as the most common drugs implicated in drug-related deaths.

Medical Comorbidities and Risk Factors

- Injection drug users are at an increased risk of HIV and Hepatitis C; treatment for opioid use is effective at reducing risk factors for HIV.
- History of substance abuse, mental health disorder, or sexual abuse are all risk factors for opioid misuse turning into opioid use disorder. Young adults age 18-25 are also at greater risk.

Psychiatric Comorbidities

- Psychiatric disorders that are especially associated with substance use disorders include: depression, anxiety, and personality disorder; suicide risk and rate are much higher among substance abusers than in the general population.
- Before starting treatment, differentiate between opioid-induced vs. opioid-independent mental health disorders and treat opioid-independent disorders in addition to the opioid use disorder
- Patients with psychiatric comorbidities are less likely to respond to opioid treatment and more likely to relapse.

PHARMACOLOGY OF BUPRENORPHINE AND OTHER OPIOIDS

Opioid Classification

- Opioids are neurotransmitter analogs and have analgesic and addictive qualities, among other effects.
- Opioids that affect mu receptors are the most important in addiction.

The Neurology of Tolerance, Withdrawal, and Physical Dependence

- Tolerance is a neurological adaptation in which sensitivity of opioid receptors decreases, requiring increasingly larger doses for the same drug effects.
- Opioid withdrawal is a severe flu-like state, with duration and severity depending on drug of abuse and degree of physical dependence.
- Dependent individuals who stop or decrease opioid use may go into *spontaneous* withdrawal.
- Dependent individuals who take an opioid antagonist may go into *precipitated* withdrawal.

Pharmacology of Buprenorphine

- Buprenorphine properties:
  - Partial mu agonist and a kappa antagonist
  - Mildly reinforcing, which contributes to effectiveness
  - Long therapeutic half-life
- Buprenorphine pharmacokinetics:
  - Rapidly absorbed through oral mucosa
  - No first pass metabolism; metabolized primarily in the gastrointestinal tract and liver
  - Partially or totally blocks the effects of abusable opioids, e.g., heroin and oxycodone
  - May precipitate withdrawal if given to a person with mu agonist (e.g., heroin) in his or her system
- Formulations: Buprenorphine/naloxone tablets or film are the formulations most widely used to treat opioid use disorder. A buprenorphine subcutaneous implant is available for moderate to low dose maintenance (8 mg or lower). Monotherapy, buprenorphine without naloxone is "a reasonable and recommended alternative to methadone for pregnant woman" (ASAM, 2015).

Evidence for the use of combination buprenorphine naloxone in pregnancy was considered "insufficient."

- Side effects:
    - Generally uncommon when taken as directed
    - Mild and can be managed by lowering the dose or waiting for tolerance to develop
    - Constipation is common; managed with diet changes and medication
- Special precautions, contraindications, interactions, adverse events
    - Low risk of overdose due to poor bioavailability and ceiling effect; risk increased by injection
    - Combination with CNS depressants, including alcohol, increases overdose risk
    - Drug interactions with benzodiazepines, sedative hypnotics, cytochrome P450 3A4 drugs, antiretroviral agents, antiseizure medications, and other opioids. Interactions include increased risk of overdose and need for dose adjustment in either direction. Consult current prescribing information.
    - Special precautions are also indicated with hepatic impairment, compromised respiratory function
    - Contraindications include head injury or intracranial lesions, hypersensitivity, elevated liver enzymes 3-5X/severe hepatic impairment, benzodiazepine abuse, alcohol use disorder or high risk, pregnancy (no combined formulation)
    - Tolerance and dependence develop more slowly to buprenorphine than to full mu agonists; buprenorphine's withdrawal syndrome is also less severe.
- Abuse potential
    - Risk for misuse, even in combination with naloxone
    - Risk of abuse is less than full mu agonists
    - Still abusable, especially by injection; combination with naloxone minimizes potential for abuse
    - As a partial agonist, buprenorphine can precipitate withdrawal in individuals with a highly physical dependence on opioids or when buprenorphine is mixed with opioid agonists; reducing the risk of buprenorphine abuse somewhat.
    - Implants may result in less diversion.

DETECTION AND DIAGNOSIS OF OPIOID USE DISORDER

Motivational Interviewing

The basic steps of motivational interviewing, which can be used to facilitate healthy behavior change in a patient, are the following:

- Engage the patient/establish rapport
- Focus the conversation on the topic
- Elicit from the patient thoughts and feelings about their substance use or quitting
- Develop a plan for change with the patient

Substance Abuse Screening

- Remain nonjudgmental, be sensitive, listen, and convey empathy.
- Routinely screen all patients for substance use disorder.

- Screening instruments can detect substance use problems more accurately than clinical judgment; e.g., CAGE-AID, can be integrated into a patient questionnaire or interview.

Signs and Symptoms of Opioid Use Disorder

- Track marks are often indicative of intravenous heroin abuse as well as psychosocial indicators.
    - Common signs and symptoms of prescription opioid misuse include:
        - Constipation
        - Low blood pressure
        - Respiratory depression
        - Mental status changes
    - Common signs and symptoms of injection use include:
        - Pupillary constriction
        - Sleepiness
        - Euphoria
        - Constipation
        - Nausea
        - Suppression of the cough reflex

Further Assessment for Substance Abusers

- Healthcare providers they are currently seeing
- What prescription drugs they take (and why)
- History of drug of addiction use:
    - Length of, severity of, and patterns of addiction
    - Tolerance, intoxication, and withdrawal
    - Abstinence and relapse
    - Consequences of use
    - Craving and control
- Treatment: medical and psychosocial

Guidelines for Assessing Adolescent Patients

- Adolescent patients should be routinely screened for substance abuse; standardized tools are available

Opioid Withdrawal

- Opioid withdrawal can begin either when opiate use ceases or is reduced or upon administration of an opiate antagonist.
- Signs and symptoms of withdrawal include:
    - Drug craving
    - Anxiety
    - Intense drug-seeking behavior
    - Yawning
    - Sweating
    - Lacrimation
    - Rhinorrhea
    - Mydriasis

- Gooseflesh
- Muscle twitching
- Anorexia
- Insomnia
- Increased pulse, respiratory rate, and blood pressure
- Abdominal cramps
- Vomiting
- Diarrhea
- Weakness

ASSESSING PATIENTS FOR TREATMENT

Assessing Patient Physical Health and Mental Health

- Assess for medical and psychiatric comorbidities as they could dramatically affect the treatment plan
- Common among patients with opioid use disorder:
    - Infectious and sexually transmitted diseases, liver and nutritional problems
    - Depression, anxiety disorders, and personality disorders

Brief interventions, provided by primary care providers, can improve patient outcomes regarding substance use disorders.
The basic steps include:

1. Confirm that the patient's screening answers indicate a concern
2. Ask about the patient's view of the situation - Includes identifying barriers to quitting and risk factors for relapse
3. Discuss the patient's personal responsibility, health effects and other consequences of substance misuse
4. Provide the patient with non-judgmental advice and describe the benefits of quitting
5. Mention treatment options and gauge patient's reaction
6. Encourage and support the patient - Includes soliciting patient commitment to a clear goal
7. Provide patient education and resources

Polysubstance Use

- Assessing for polysubstance use before starting buprenorphine is important due to potentially harmful or even fatal interactions with some licit and illicit drugs
- Polysubstance use screening can be conducted using screening forms, patient examination and interview, and urine drug tests.

Determining Appropriateness for Buprenorphine Treatment

- Factors associated with a positive response to buprenorphine treatment:
    - Patient knowledge and interest
    - Practice resources
    - Supportive psychosocial circumstances
    - Absence of interacting prescriptions
    - Opioid use disorder

    - Psychiatric stability including compliance with medications
- Patients who resist quitting drug use may benefit from motivational interviewing techniques that increase the patient's readiness for change through a series of basic steps:
    - Introduce the topic
    - Assess motivation
    - Evaluate ambivalence
    - Plan for change
- Do not discount a patient as a candidate just because one of the contraindicated factors is present. Weigh these factors against positive indications.
- Create a treatment plan with input from the patient.

INDUCTION

Indicated Use of Buprenorphine

- Buprenorphine treatment phases are:
    - Induction
    - Stabilization
    - Maintenance

Formulations

- Buprenorphine is available as buprenorphine/naloxone combination therapy; the form that should be prescribed for most patients, and buprenorphine monotherapy
- Sublingual film, buccal film, or sublingual tablet are available currently

General Induction Guidelines

- Induction can be conducted in the office or at home. Consider that the "Appropriate Use" checklist published by the FDA includes "Provided induction doses under appropriate supervision" and that some patients may need the guidance and monitoring of an in-office visit.
- Patients should be in mild/moderate withdrawal (COWS score of 12-16), typically achieved by 12 to 16 hours of abstinence if dependent on short-acting opioids, 17-24 hours for intermediate acting, and 30-48 hours for methadone and other long acting opioids (Gunderson, 2014).
- Initial dose is 2 mg to 4 mg buprenorphine, typically with the corresponding dose of naloxone.
- Monitor the patient for around 1+ hour for response to dose should occur at induction, followed by increments of 2 to 4 mg, followed by another 1 + monitoring.
- Maximum dose day 1 is 16 mg
- Follow-up by phone that day and for each day of induction until the maintenance dose is established
- Recommended maintenance daily dose is 4 to 24 mg (Gunderson, 2014). Most commonly, the maintenance dose is 12 to 16 mg (Suboxone or equivalent doses for Zubsolv or Bunavail), which is as effective as 60 mg of methadone.
- After maintenance dose is established, have an office visit in 3-4 days
- Dose adjustments potentially occur during all 3 phases of treatment, but are far less common after induction.

Standard Induction Protocol

- First day maximum dose can range from 8-16 mg (Suboxone® or equivalent doses for Zubsolv® or Bunavail®), given in 4 mg increments.
- After day 1, dose can be increased a maximum of 8 mg per day, to a ceiling dose of 32 mg.
- Daily dose is established when the patient is neither undermedicated nor overmedicated. Average daily dose is 16 mg.
- During induction, treat withdrawal symptomatically.

Stabilization

- The stabilization period lasts several weeks following induction. Patients should receive a limited supply of medication during stabilization and return for regular follow-up, weekly for the first month.

Medically Supervised Withdrawal

Buprenorphine can be used to ease acute symptoms of withdrawal for patients who want complete detoxification followed by taking no medication assisted treatment or opioids. It generally has poorer success rates than continued medication-assisted treatment.

MAINTENANCE AND DISCONTINUATION

Buprenorphine Maintenance Guidelines

- Buprenorphine maintenance should continue indefinitely for most patients; unless there is a compelling reason to stop, due to the high rate of relapse when buprenorphine is discontinued.
- Concurrent and psychosocial support is an important part of treatment. Periodic psychosocial assessment is indicated throughout treatment.
- Maintenance dose with no withdrawal and no cravings is between 12-16 mg (Suboxone® or generic, slightly less for Zubsolv® or Bunavail®) for most patients.
- Conduct lab tests and periodic psychosocial assessments throughout the maintenance phase.
- The buprenorphine implant is an alternative for patients who have been maintained on a stable dose of 8 mg or less for at least 3 months. It is placed under the skin in a minor surgical procedure by a REMS-certified prescriber and replaced every 6 months.

Tapering Off of Buprenorphine

- If patients wish to discontinue buprenorphine use, alternative forms of pharmacotherapy may be their best chance for remaining abstinent.
- A gradual taper, usually over a period of around 2 weeks, is used for discontinuation of buprenorphine.
- Shorter and longer tapers are safe and can be used if needed, based on circumstance.
- Patients should be monitored carefully for signs of withdrawal if tapered off buprenorphine.

Relapse

- Relapse is common among addiction patients and usually should not be ground for dismissal from a treatment program.
- Relapse may mean that a higher dose or more intensive psychosocial treatment is needed.

Treating Pain in Patients on Buprenorphine for Opioid Use Disorder

- Detoxification is not as effective as long-term medication maintenance treatment, with buprenorphine, for example, in helping patients stay otherwise opioid-free over the long-term.
- Patients in detoxification should be carefully monitored, offered appropriate psychosocial support, and offered medication maintenance treatment, such as buprenorphine, if they become unstable.
- Patients on buprenorphine who develop moderate to severe pain should be treated with non-opioids if possible. If that is not possible, a careful regimen may be followed to safely treat their pain with opioids.
- Patients with chronic pain who require opioid replacement therapy could be maintained on methadone rather than buprenorphine.

METHADONE PATIENTS AND OTHER SUBPOPULATIONS

Guidelines for Transferring Methadone Patients to Buprenorphine

- The *pre-induction protocol* differs slightly for treatment of long-acting (methadone) vs. short-acting opioid dependence.
- Patients who are seeking a transfer from methadone to buprenorphine should be carefully evaluated and advised about what to expect during induction and maintenance.
- Methadone patients should be tapered down to a 30 mg daily dose just prior to transfer and maintained on this dose for a week.

Induction Protocol for Methadone Patients

- Patients on high doses of methadone (60+ mg) may experience significant pain or discomfort during tapering, which puts them at risk for relapse.
- Patients need to abstain from methadone for 36-72 hours before their first dose of buprenorphine. They should be in mild to moderate withdrawal, as determined by the COWS.
- Buprenorphine *dosing guidelines* are the same for long-acting and short-acting opioids, although some clinicians start methadone transfers at lower doses (2 mg Suboxone®/generic or equivalent) to decrease the risk of precipitated withdrawal.

Buprenorphine Considerations for Other Special Patients

- Special considerations for adolescents, pregnant women, elderly patients, patients with viral hepatitis or HIV, and psychiatric patients should be consulted before treating these groups with buprenorphine.
- Buprenorphine is safe to use with most psychiatric medications, though benzodiazepines should be prescribed with a high level of caution and patients should be monitored closely.

MANAGING PATIENTS IN A BUPRENORPHINE PRACTICE

Recommendations for Defining Practice Rules and Expectations

- Create a set of rules and expectations to apply to all patients that are mutually agreeable and defined during the initial visit.

Recommendations Related to Buprenorphine Treatment

- Discuss all aspects of buprenorphine treatment

- Prescribe only small amounts of buprenorphine for new patients and provide refills if they are compliant with treatment.
- Be aware of all drugs and medications currently being used by patients.

Dealing with Problematic Behaviors

- Most office-based opioid treatment patients are compliant with treatment, but be aware of problematic behaviors and have a plan for dealing with them.
- Patients who are taking buprenorphine but still abusing opioids or other drugs may need to be referred to a higher level of care.

Dealing with Misuse and Diversion of Buprenorphine

- Missed appointments, lost prescriptions, and inaccurate pill counts are among the signs that buprenorphine is being misused or diverted.
- Patients who misuse or divert their medication should be reevaluated and moved to a more intensive level of treatment if needed.

Enforcing Consequences for Negative Behaviors

- Violations of the treatment agreement or practice rules must be addressed
- Place each violation in the context of that individual's condition
- Consider if more intensive treatment is required
- Serious negative behaviors are grounds for discharge from the practice.

Urine Testing in Buprenorphine Treatment

- Urine drug testing should be routine in an opioid treatment program.
- Randomized testing with direct observation is most effective.
- Interpret results cautiously. Do not assume a negative test means a patient is not taking drugs. Likewise, a positive result is not necessarily definitive.

REGULATIONS FOR OFFICE-BASED OPIOID TREATMENT

A Team Approach to Office-Based Treatment

Using a team approach with trained staff is important for office-based opioid treatment, in order to:

- Provide patients who need it with additional time and support.
- Train staff to address prejudice and prepare them to deal with aberrant behavior by some patients.
- To assure that staff understand confidentiality rules and the rules for office based opioid treatment, such as refill policies.

Confidentiality of Patient Records

The Public Health Service Act, Title 42 of the United States Code of Federal Regulations, governs laws in substance abuse treatment (SAMHSA, 1994a). These regulations are meant to prevent the disclosure of information identifying applicants/recipients of substance abuse treatment. They prohibit the release of patient records without:

- Patient consent
- A court order
- A true medical emergency

- Or report of child abuse

It is very important to abide by the confidentiality regulations. Violation carries a criminal penalty of $500 for the first violation and $5,000 for each successive violation. Patients may also file lawsuits if their confidentiality is violated. Program-level violations may result in revoking of license or certification.

Billing and Insurance

Prior to starting a patient on buprenorphine, discuss the issue of payment for services, including who should be billed: an insurance agency, the patient, or both.

- **Insurance:** Become familiar with the billing codes, as well as what can and cannot be billed for service. Document billable hours.
- **Patient:** Arrange a payment schedule and note what costs the patient will incur for treatment. Provide an itemized estimate of medication plus office-visit costs.
- **Both:** Determine what costs will be billed to the insurance company vs. the patient. Clarify patient responsibilities versus what their insurance will cover.