Medication-Assisted Treatment (MAT) & What It Means Long-Term

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"Methadone is the Gold Standard for treatment of chronic heroin addiction"

Narcotics and Opioids

- Narcotics: those drugs which possess both an analgesic (pain relieving) and sedative properties.
- Opioid refer to drugs in a generic sense, natural or synthetic, with morphine- like actions

History of Buprenorphine

- Federal statute, the Drug Addiction Treatment Act of 2000 (DATA 2000), has established a new paradigm for the medication-assisted treatment of opioid addiction in the United States (Drug Addiction Treatment Act of 2000).
- In October 2002, FDA approved two sublingual formulations of the Schedule III opioid partial agonist medication buprenorphine for the treatment of opioid addiction.

Regulatory Issues

- DATA 2000 – physicians can use schedule III, IV, V meds in other than OTPs
- Suboxone and Subutex approved FDA 2002 – approved for the treatment of opioid dependence
- Interim Final Rule 2003 – approval to use Suboxone/Subutex in OTP

History of Buprenorphine

- Subutex® (buprenorphine) and Suboxone® (buprenorphine/naloxone), are the first and the only Schedule III, IV, or V medications to have received such FDA approval and, thus, to be eligible for use under DATA 2000.
- More than 20 years ago, buprenorphine was identified as a viable option for the maintenance treatment of individuals addicted to opioids.

Pharmacotherapy Treatment Options for Opioid Addiction

- Three traditional types of pharmacotherapy for opioid addiction:
  1. agonist treatment (e.g., methadone pharmacotherapy)
  2. antagonist treatment (e.g., naltrexone)
  3. the use of these and other agents (e.g., clonidine)

Opioid Receptors

- Types of opioid receptors:
  - Mu--mu agonist causes respiratory depression, pupillary constriction, and euphoria.
  - The addictive effects of opioids occur through activation of mu receptors.
  - Kappa--Kappa activation produces analgesia
  - Delta--There are no prototypic delta agonists studied in humans,

Available Medications for Treatment of Heroin/Opiate Addiction

- Agonists — Opiate Analgesics
  Methadone
  LAAM
- Partial Agonists — Buprenorphine
- Antagonists — Naloxone (short-acting)
  Naltrexone (long-acting)

- Agonist
  - **Heroin, Morphine, Codeine, Methadone, LAAM**
  - Mild-moderate binding to mu receptors
  - Short-acting = Powerful opiate high
  - Long-acting = Weak opiate high
- Partial Agonist
  - **Buprenorphine**
  - Strong and long binding to mu receptors
  - *But …* Relatively weak opiate effect
- Antagonist
  - **Naloxone, Naltrexone**
  - Strong binding to mu receptors but does not activate them
  - Thus, blocks all opiates with no opiate effects

General Pharmacology of Opioid Agonists and Antagonists

- Opioid *agonists*--Drugs that activate opioid receptors on neurons.
  - Heroin and methadone are opioid agonists.
- Opioid Antagonists--Opioids that bind to opioid receptors but block them, rather than activating them.
  - Examples of opioid antagonists are naltrexone and naloxone.

Opioid Receptors

- Drugs and medications that activate mu receptors:
  - morphine
  - heroin
  - methadone
  - LAAM
  - hydromorphone
  - buprenorphine
  - codeine
  - Fentanyl
    - These are not all the medications that can activate the mu receptor.

Functions of Drugs at Receptors

- Full agonists:
- Occupy the receptor and activate that receptor
  - Increasing doses of the drug produce increasing receptor-specific effects until a maximum effect achieved
- Most abused opioids are full agonists
- Examples of full agonist opioids: heroin, LAAM, methadone, morphine

Functions of Drugs at Receptors

- Partial agonists:
  - Bind to and activate receptor
  - At lower doses, a partial agonist and a full agonist produce similar effects.
  - However, as the dose of a partial agonist is increased, the effect produced does not increase. There is less of a maximal effect – no matter how much the dose is increased.
- Buprenorphine is a partial mu agonist opioid

Functions of Drugs at Receptors

- Antagonists:
  - Bind to receptors but don't activate the receptor
  - By occupying a receptor, it prevents other drugs such as agonists from occupying and activating that receptor
  - Block the receptor from activation by full and partial agonists
- Examples of opioid antagonists are naloxone (Narcan), naltrexone (ReVia), and nalmefene.

Functions of Drugs at Receptors

- In a person who is not physically dependent upon opioids, an antagonist produces no effects.
- In a person who is dependent upon opioids, an antagonist can precipitate withdrawal
- In a person maintained on an antagonist, administration of a full or partial agonist does not result in an effect from the agonist. This is because the antagonist blocks the receptor.

Withdrawal Stages for Short Acting Opioids

- Anticipatory (3-4 hours after last use)
  - Signs and symptoms: fear of withdrawal, anxiety, drug-seeking behavior
- Early (8-10 hours after last use)
  - Signs and symptoms: anxiety, restlessness, yawning, nausea, sweating, nasal stuffiness, rhinorrhea, lacrimation, dilated pupils, stomach cramps, drug-seeking behavior
- Fully-developed (1-3 days after last use)
  - Signs and symptoms: severe anxiety, tremor, restlessness, piloerection, vomiting, diarrhea, muscle spasm, muscle pain, increased blood pressure, tachycardia, fever, chills, impulse-driven drug-seeking behavior

Rationale for Opioid Agonist Medications

- Opioid agonist maintenance treatment
- Targets biological factors perpetuating heroin administration
- Prevents withdrawal
- Reduces craving
- Blocks or attenuates euphoric effects of exogenous opioids
- When properly dosed and managed, methadone (and LAAM and buprenorphine) prevents opioid withdrawal, reduces craving, and blocks or attenuates the euphoric effects of other opioids such as heroin.

Subutex® and Suboxone®

- **Two, schedule III, sublingual buprenorphine tablet formulations (2 mg and 8 mg) approved for US use:**
  - **Subutex® (buprenorphine alone)**
  - **Suboxone® (buprenorphine + naloxone)**
    - **In contrast, methadone is a schedule II drug**
- **Partial mu-opioid agonists**
- **Suboxone® is the focus of US marketing efforts**

What are Subutex and Suboxone?

- Subutex and Suboxone are medications approved for the treatment of opiate dependence. Both medicines contain the active ingredient, buprenorphine hydrochloride, which works to reduce the symptoms of opiate dependence.
  - Subutex contains only buprenorphine hydrochloride. This formulation was developed as the initial product.
  - Suboxone contains an additional ingredient called naloxone to guard against misuse. Subutex is given during the first few days of treatment, while Suboxone is used during the maintenance phase of treatment.

Subutex

- SUBUTEX sublingual tablets contain buprenorphine HCl.
- SUBUTEX is an uncoated **oval white tablet** intended for sublingual administration. It is available in two dosage strengths, 2mg buprenorphine and 8mg buprenorphine free base.
- Each tablet also contains lactose, mannitol, cornstarch, povidone K30, citric acid, sodium citrate and magnesium stearate

Suboxone

- SUBOXONE is an uncoated **hexagonal orange tablet** intended for sublingual administration.
- It is available in two dosage strengths, 2mg buprenorphine with 0.5mg naloxone, and 8mg buprenorphine with 2mg naloxone free bases.
- Each tablet also contains lactose, mannitol, cornstarch, povidone K30, citric acid, sodium citrate, FD&C Yellow No.6 color, magnesium stearate, and the tablets also contain Acesulfame K sweetener and a lemon / lime flavor.

Buprenorphine is <u>not</u> a substitute for methadone, it is one more choice on the treatment menu.

Both are medications which should be used in comprehensive treatment

Some possible side effects of Subutex and Suboxone

- Most common reported side effect of Subutex and Suboxone include:
  - cold or flu-like symptoms
  - headaches
  - sweating
  - sleeping difficulties
  - nausea
  - mood swings

Some possible side effects of Subutex and Suboxone

- Like other opioids Subutex and Suboxone have been associated with respiratory depression (difficulty breathing) especially when combined with other depressants.

Buprenorphine

- Buprenorphine is a partial agonist at the mu-opioid receptor and an antagonist at the kappa-opioid receptor. Naloxone is an antagonist at the mu-opioid receptor.
- Buprenorphine is a Schedule III narcotic under the Controlled Substances Act.
- At low doses Buprenorphine is an opioid agonist.
- At high doses it is an opioid antagonist.

Pharmacology of Buprenorphine

- Buprenorphine a thebaine derivative
  - Thebaine is an alkaloid from opium. This is important, because it leads to buprenorphine's legal classification as an opioid.
- High potency
- Available as a parenteral analgesic
- Produces sufficient agonist effects to be detected by the patient
- Used outside United States for the treatment of opioid dependence

Pharmacology of Buprenorphine

- Buprenorphine is mildly reinforcing, which means that an opioid-experienced person detects an effect with buprenorphine. (This is unlike a pure opioid antagonist, like naltrexone.)
- Clinically, this is desirable because it means patients are motivated to reliably maintain themselves on buprenorphine – unlike opioid antagonist maintenance

Pharmacology of Buprenorphine

- Buprenorphine has high affinity for the mu opioid receptor. This means that it is hard for other opioids with lower affinity to displace buprenorphine from the mu receptor (so it blocks their effects
  - The strength with which a drug binds to a receptor is referred to as its "affinity."
- Buprenorphine's slow dissociation from the mu receptor results in a prolonged therapeutic effect. Considerable evidence suggests buprenorphine can be given three times per week (rather than daily), and there is some evidence suggesting buprenorphine can be given even less frequently (e.g., two times per week).

Some of the Effects of Buprenorphine

- Buprenorphine has a very high affinity for mu receptors. Thus, it displaces morphine, methadone, and other full agonist opioids from the receptor.
- Buprenorphine dissociates slowly from the mu receptor. Thus, it is able to block the effects of other opioids, such as heroin.
- A very slow dissociation rate from the mu receptor gives rise to buprenorphine's prolonged therapeutic effects.

Pharmacology of Buprenorphine: Bioavailability

- Good parenteral bioavailability
- Poor oral bioavailability
- Fair sublingual bioavailability
- For opioid dependence treatment:
  - early clinical trials used an alcohol-based solution
  - FDA approval for tablets that are held under tongue

Abuse Potential

- Buprenorphine is abusable (epidemiological, human laboratory studies show)
- Diversion and illicit use of analgesic form (by injection)
- Relatively low abuse potential compared to other opioids

Outcomes from Buprenorphine Research

- Buprenorphine is equally effective as moderate doses of methadone (such as 60 mg per day) on primary outcome measures.
- 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).
- Buprenorphine appears to be equally effective as moderate doses of LAAM (such as 70 mg/70 mg/85 mg on a Monday, Wednesday, and Friday schedule).

Outcomes from Buprenorphine Research

- Buprenorphine's partial *mu* agonist properties make it mildly reinforcing, which encourages good patient compliance for regular medication ingestion.
- After a year of buprenorphine plus counseling, as many as 75 percent have been retained in treatment compared to none in a placebo-plus-counseling condition

Naltrexone Pharmacology

- Opioid antagonist (no effects in non-dependent person, precipitated withdrawal in opioid dependent person)
- No agonist properties; no reinforcing effects to add to the patient's motivation to continue taking naltrexone
- Effectively blocks effects of opioids (e.g., heroin)
- Good oral bioavailability
- Long duration of action

Naltrexone Efficacy

- Highly effective in controlled, inpatient studies
- Can be taken daily or three times per week
- Compliance and treatment retention are poor in general in outpatient clinical trials
- Compliance is better in motivated patients (e.g., physicians, business professionals)

Naltrexone Safety and Side Effects

- Very safe in usual dose range
- Higher than usual doses may produce increases in liver function tests (LFTs)
- Most commonly reported side effects are abdominal complaints and dysphoria (although both are rare)

Government Regulation of Naltrexone Treatment

- Not scheduled; no abuse potential
- No special regulations governing naltrexone use

Phases of Buprenorphine Treatment

- **Dose induction and stabilization**
- Maintenance
- Medically-supervised withdrawal

Rapid and direct dose Induction: Short-Acting Opioids

- Patients taking short-acting opioids (e.g., heroin) can be placed directly on Suboxone®
- Most patients complete induction and can achieve a stable dose of medication within 7days
- Induction should be rapid and doses adjusted to clinical need as quickly as possible to reduce withdrawal and craving and prevent early drop-out

Induction from Long-Acting Opioids (Methadone)

- More controlled data are needed to determine optimal strategies for Crossover
- Current US guidelines recommend lowering dose to the equivalent of about 40 mg of methadone before attempting to transfer
- Physicians should not necessarily refuse to treat patients on higher doses of methadone or require a substantial lowering of their current medication dose before attempting transfer

Maintenance Considerations

- We should consider buprenorphine as a maintenance drug
- Regulations must be brought into alignment with clinical opportunity
- Flexibility of dosing: 3X/wk dosing

Medically supervised withdrawal

- Good agent for pharmacologic withdrawal from opioids
  - slow dissociation from receptor, extended duration of action, less/milder withdrawal when discontinued
- Research more limited in this area but we do know:
  - Subutex®/Suboxone® better than clonidine
  - Ancillary medications should be made available but not always necessary
- May help attract more patients into treatment

Effective Medically Supervised Withdrawal should:

- Be the initial step in a treatment continuum
- Safely control symptoms of withdrawal
- Engage patients through out the actual withdrawal insuring completion
- Facilitate their transfer into long term treatment

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Medically supervised withdrawal: Summary

- Short-term supervised withdrawal using Suboxone® and ancillary medications is safe, can maintain good during-treatment compliance and retain patients through the end of the dose taper
- Such programs may improve early treatment engagement among patients resistant to maintenance therapy and may provide a gateway to longer-term care
- May be a good first-line option for younger users, those with limited treatment histories and/or patients who initially refuse maintenance therapy

Evidence support: Summary

- Safe, well-tolerated, effective and clinically flexible treatment with low abuse potential
- Good option for maintenance and medically supervised withdrawal
- Easily integrated into diverse settings (OTP, office, hospital, residential, drug-free, etc.)
- Potential for enhancing management of special populations
- As knowledge about buprenorphine expands within OTPs, patient interest also likely to increase

Patients able to take Home Supplies

- Subutex and Suboxone are less tightly controlled than methadone because they have a lower potential for abuse and are less dangerous in an overdose.
- As patients progress on therapy, their doctor may write a prescription for a take-home supply of the medication.

Key Components of the Risk-Management Plan

- The main components of the risk-management plan are preventive measures and surveillance:
- Surveillance
  - Conduct interviews with drug abusers entering treatment programs.
  - Monitor local drug markets and drug using network areas where these medicines are most likely to be used and possibly abused.
  - Examine web sites.

Key Components of the Risk-Management Plan

- The main components of the risk-management plan are preventive measures and surveillance:
- Preventive Measures include:
  - education
  - tailored distribution
  - Schedule III control under the Controlled Substances Act (CSA)
  - child resistant packaging
  - supervised dose induction

Counselors: Opioid addiction and the Brain

- Opioids attach to *mu* opioid receptors in the brain.
- This activation of the receptor results in pleasure.
- After repeated opioid use, the brain becomes altered. More opioid is required to produce the desired effect (tolerance). When opioids are absent from the brain, there is a discomfort (withdrawal) that drives the person to ingest more opioids to alleviate the distress.

The Safety Profile of Buprenorphine

- Very little of it reaches systemic circulation after swallowing is an added safety feature.
- When administered sublingually as properly instructed, it is absorbed through the mucosa and does not go thru the gastrointestinal track, as is the case when the medication is sucked or chewed and swallowed, or simply swallowed.

Primary Side Effects of Buprenorphine

- Primary side effect is an increase in tolerance.
  - Its intensity may be less than those produced by full agonist opioids, such as methadone and heroin.
- Respiratory Depression
  - Contrast to full mu agonists, buprenorphine overdose does not appear to produce lethality (in noncompromised persons) through respiratory depression.
  - Avoid combining it with other CNS depressants

Primary Side Effects of Buprenorphine

- Safety and Use in Pregnancy
  - There is limited clinical experience with buprenorphine maintenance in opioid-dependent pregnant women. The research literature consists primarily of case reports.
- Precipitated Withdrawal
  - Under certain circumstances (such as in buprenorphine induction), it can precipitate the opioid withdrawal syndrome in a person with a high degree of physical dependence. This might occur in an individual maintained on more than 30 to 40 mg of methadone daily.

Primary Side Effects of Buprenorphine

- **Overdose**
  - Buprenorphine overdose has a low likelihood of clinically significant problems, especially with regard to respiratory depression.
- Psychomotor, Cognitive Performance, and Other Effects
  - Available evidence in patients maintained on buprenorphine indicates no clinically significant disruption in cognitive and psychomotor performance (Walsh et al. 1994).

Appropriateness for Office-Based Treatment: 10 Factors

- Does the patient have a diagnosis of opioid addiction?
- Is the patient interested in office-based buprenorphine treatment?
- Is the patient aware of the other treatment options?

Appropriateness for Office-Based Treatment: 10 Factors

- Does the patient understand the risks and benefits of buprenorphine treatment and that it will address some aspects of the substance use (for example, withdrawal suppression and blockade) but not all aspects (such as triggers and cravings that may be elicited by events and circumstances in the environment)?

Appropriateness for Office-Based Treatment: 10 Factors

- Is the patient expected to be reasonably compliant? Are there indicators from his or her life that suggest he or she is reliable, such as steady employment, following through in taking medications for other medical conditions, or showing up on time for office appointments?

Appropriateness for Office-Based Treatment: 10 Factors

- Is the patient expected to follow safety procedures?
- Is the patient psychiatrically stable?
- Are the psychosocial circumstances of the patient stable and supportive?

Appropriateness for Office-Based Treatment: 10 Factors

- Are there resources available in the office to provide appropriate treatment? Are there other physicians in the group practice? Are there treatment programs available that will accept referral for more intensive levels of service?
- Is the patient taking other medications that may interact with buprenorphine, such as naltrexone, benzodiazepines, or other sedative-hypnotics?

Appropriateness for Office-Based Treatment: Lower Likelihood

- Addiction to high doses of benzodiazepines, alcohol, or other central nervous system depressants
- Significant psychiatric comorbidity
- Active or chronic suicidal or homicidal ideation or attempts
- Multiple previous opioid addiction treatment episodes with frequent relapse during those episodes

Appropriateness for Office-Based Treatment: Lower Likelihood

- Non-response or poor response to buprenorphine treatment in the past
- High level of physical dependence on opioids
- Patient needs that cannot be addressed with existing office-based resources or through appropriate referrals
- High risk for relapse to opioid use (for example, living in a place where heroin is consumed)
- Pregnancy
- Poor support system.

Appropriateness for Office-Based Treatment: Medical Contraindications

- Seizures. Seizures can occur with some opioids; however this is not the case with buprenorphine.
- HIV and STDs. The concern is that patients with these conditions often take a variety of medications and there is a potential for a medication interaction.
- Hepatitis and impaired hepatic function. The possibility of a medication interaction is the concern here also.

Appropriateness for Office-Based Treatment: Medical Contraindications

- Pregnancy. There is no evidence of any harmful effects of buprenorphine relative to pregnancy, but in the absence of controlled clinical trials, risk cannot be ruled out. Pregnant patients should be strongly considered for methadone rather than buprenorphine treatment.
- Use of alcohol, sedative-hypnotics, and stimulants.

Appropriateness for Office-Based Treatment: Medical Contraindications

- **Other drugs.** Buprenorphine is a treatment for opioid addiction, not other drug abuse disorders. Patients who abuse more than one substance present unique problems. Abuse of or addiction to other drugs (such as stimulants or sedatives) is common among opioid-addicted persons and may interfere with overall treatment adherence.

Counseling Issues

- Orienting buprenorphine patients to recovery
- Recovery and pharmacotherapy
- 12-Step meetings

Nursing Staff: Precipitated Withdrawal and Withdrawal Symptoms

- Precipitated withdrawal is more likely to occur with higher levels of opioid dependence, with short-time intervals (e.g., less than 2 hours) between a dose of a full opioid agonist and a dose of buprenorphine, and with higher doses of buprenorphine.
- Buprenorphine can precipitate an opioid withdrawal syndrome if administered to a patient who is opioid dependent and whose receptors are currently occupied by opioids.

Nursing Staff: Precipitated Withdrawal and Withdrawal Symptoms

- A patient should no longer have any residual opioid effect from his or her last dose of opioid before receiving a first dose of buprenorphine.
- Due to this required abstinence before the initiation of buprenorphine treatment, it is likely that patients will feel that they are experiencing the early stages of withdrawal when they present for buprenorphine induction treatment.

Nursing Staff: Helping Patients Manage Mild Withdrawal Symptoms

- Patients who are physically dependent on methadone or other long-acting opioids must be carefully selected for buprenorphine therapy.
- Appropriate patients may include those who have had difficulty adhering to scheduled visits at OTPs due to personal conflicts and work schedules or travel, as opposed to those who have been noncompliant with methadone treatment appointments.

Nursing Staff: Helping Patients Manage Mild Withdrawal Symptoms

- Patients who are stable on methadone maintenance and who do not have a compelling reason to switch therapy should continue methadone maintenance because of the elevated risk for precipitated withdrawal during the conversion from methadone to buprenorphine.

Nursing Staff: Three Phases of Buprenorphine Therapy

- **Induction phase.** The induction phase is the medically monitored and supervised start-up of buprenorphine therapy.
  - The goal of induction is to find the minimum dose at which the patient markedly reduces or eliminates use of other opioids and experiences no withdrawal symptoms, side effects, or cravings.
  - It may be particularly helpful to ask patients about their typical first three signs of withdrawal and when they occur.

Nursing Staff: Three Phases of Buprenorphine Therapy

- **Stabilization phase.** The stabilization phase begins when patients who have discontinued or greatly reduced the use of their drug of abuse no longer have cravings and are experiencing few or no side effects.
- **Maintenance phase.** The maintenance phase is reached when the patient is doing well on a steady dose of buprenorphine (preferably Suboxone®, the buprenorphine and naloxone combination product).

Buprenorphine: A Guide for Nurses

References

- Buprenorphine: A guide for nurses (Tip 30)
- Buprenorphine Treatment of Opioid Addiction: A Guide for Counselors by Dana Learning Center