Module I
The Science and The Law

This module will review...
- Epidemiology
- Drug Addiction Treatment Act of 2000
- Opioid neurobiology and pharmacology
- Treatment with medications

Past Month and Past Year Heroin Use: 2002-2013

Prescription Opioid Trends: 1999-2010

Opioid Overdose Trends: 2000-2013

Drug Addiction Treatment Act of 2000
- Allows a waivered physician (DEA "X" number) to prescribe an opioid to a patient with an opioid use disorder for the treatment of the opioid use disorder, with certain restrictions
**Opioid Pharmacology**

- **Opiates and Opioids**
  - Opiates are present in opium e.g. morphine, codeine, thebaine
  - Opioids are manufactured as
    - Semi-synthetic opioids derived from an opiate e.g. heroin from morphine
    - Synthetics opioids completely synthesized to have function similar to natural opiates e.g. methadone

- **Reward/Reinforcement**
  - Reward/Reinforcement is in part controlled by mu receptors in the Reward Pathway:
    - Ventral Tegmental Area (VTA)
    - Nucleus Accumbens with projections to Prefrontal Cortex
    - Dopaminergic system

- **DATA 2000, restrictions:**
  - Physicians qualifications
    - Certified in addiction medicine/psychiatry, or
    - have 8 hours of training by AMA, AAP, ASAM, AOA, APA
    - Certify capacity to refer the patients for appropriate counseling and other appropriate ancillary services
  - Medication qualifications
    - Approved by FDA for use in treating addiction
    - DEA schedule III, IV, or V (methadone is schedule II)
    - Buprenorphine and Buprenorphine/naloxone SL tablets and film FDA approved and DEA schedule III, and are the only medications fitting these restrictions

- **DATA 2000 restrictions: number of patients**
  - 30 patients per physician during the first year of the waiver
  - After the first year 100 patients per physician – a new waiver must be obtained
  - Patient remains on your census until the last prescription has run out
  - Hospitalized patients with a primary diagnosis of other than opioid dependence can be prescribed buprenorphine by a non-waivered physician

- **Opioid Tolerance & Physical Dependence**
  - Both tolerance and physical dependence are physiological adaptations to chronic opioid exposure
  - **Tolerance:**
    - Increased dosage needed to produce specific effect
    - Develops readily for CNS and respiratory depression
  - **Physical Dependence:**
    - Signs and symptoms of withdrawal by abrupt opioid cessation, rapid dose reduction
Natural History of Opioid Use Disorder

Acute use
- Normal
- Euphoria
- Withdrawal
- Tolerance & Physical Dependence

Chronic use

Acute Opioid Withdrawal

<table>
<thead>
<tr>
<th>Grade</th>
<th>Symptoms</th>
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</thead>
<tbody>
<tr>
<td>0</td>
<td>Anxiety, Drug Craving</td>
</tr>
<tr>
<td>1</td>
<td>Yawning, Sweating, Runny nose, tearing, Restlessness, Insomnia</td>
</tr>
<tr>
<td>2</td>
<td>Dilated pupils, gooseflesh, Muscle twitching &amp; shaking, Muscle &amp; joint aches, loss of appetite</td>
</tr>
<tr>
<td>3</td>
<td>Nausea, extreme restlessness, elevated blood pressure, Heart rate &gt; 100, Fever</td>
</tr>
<tr>
<td>4</td>
<td>Vomiting, dehydration, Diarrhea, Abdominal cramps, curled-up body position</td>
</tr>
</tbody>
</table>

Clinical Opiate Withdrawal Scale (COWS):
- pulse, sweating, restlessness & anxiety, pupil size, aches, runny nose & tearing, GI sx, tremor, yawning, gooseflesh
- mild (1-4), moderate (5-12), severe (13-24)

Spontaneous Acute Opioid Withdrawal

- Develops spontaneously in a physically opioid dependent person suddenly stops or markedly decreases the opioid
- Severity is usually less with longer half-life drugs
- Duration depends on half-life of opioids person uses

<table>
<thead>
<tr>
<th>Drug</th>
<th>Onset</th>
<th>Peak</th>
<th>Duration</th>
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<tr>
<td>Heroin</td>
<td>4-6 hours</td>
<td>~3 days</td>
<td>4-7 days</td>
</tr>
<tr>
<td>Methadone</td>
<td>1-2 days</td>
<td>~7 days</td>
<td>12-14 days</td>
</tr>
</tbody>
</table>

Precipitated Acute Opioid Withdrawal

- Precipitated in a physically opioid dependent person, by administration of either:
  - an opioid antagonist drug (e.g. naloxone, naltrexone) or
  - an opioid partial agonist drug (e.g. buprenorphine)
- Qualitatively similar to spontaneous withdrawal but faster onset
- Duration depends upon half-life of drug

<table>
<thead>
<tr>
<th>Drug</th>
<th>Onset</th>
<th>Peak</th>
<th>Duration</th>
</tr>
</thead>
<tbody>
<tr>
<td>Naloxone</td>
<td>minutes</td>
<td>minutes</td>
<td>~30 minutes</td>
</tr>
<tr>
<td>Naltrexone</td>
<td>minutes</td>
<td>minutes</td>
<td>1-2 days</td>
</tr>
<tr>
<td>Buprenorphine</td>
<td>minutes</td>
<td>minutes</td>
<td>1-2 days</td>
</tr>
</tbody>
</table>

Precipitating Acute Withdrawal

- Buprenorphine will precipitate withdrawal when it displaces full agonist off the mu receptors

- A Net Decrease in Receptor Activity if a Partial Agonist Displaces Full Agonist

Opioid Agonists and Antagonists
Low rates of retention in treatment
High rates of relapse post-treatment
- < 50% abstinrent at 6 months
- < 15% abstinent at 12 months
- “Detox” is not treatment, it is just the start of treatment
Increase rates of overdose due to decreased tolerance

Protracted abstinence syndrome (chronic withdrawal)
- Generalized malaise, fatigue, insomnia
- Poor tolerance to stress and pain
- Opioid craving
- Conditioned cues (triggers)
- Priming with small dose of drug

Oral Naltrexone Efficacy
- Oral naltrexone
- Duration of action 24-48 hours
- FDA approved 1984
- 10 RCTs ~700 participants to naltrexone alone or with psychosocial therapy compared with psychosocial therapy alone or placebo
- No clear benefit in treatment retention or relapse at follow up
- Benefit in highly motivated patients
- Impaired physicians > 80% abstinence at 18 months

Medically Supervised Withdrawal “Opioid Detoxification”
- Goals
  - Alleviate signs/symptoms of physical withdrawal
  - Opioid receptor blockade
  - Diminish and alleviate drug craving
  - Normalize and stabilize perturbed brain neurochemistry
- Options
  - Opioid Antagonist
    - Naltrexone (full opioid antagonist)
  - Opioid Agonist
    - Methadone (full opioid agonist)
    - Buprenorphine (partial opioid agonist)

Injectable Naltrexone (XR-NTX)*
- Multicenter (13 sites in Russia) Funded by Alkermes
- DB RPCT, 24 wks, n=250 w/ opioid dependence
- XR-NTX vs placebo, all offered biweekly individual drug counseling
- Weeks of confirmed abstinence (90% vs 35%)
- Patients with confirmed abstinence (36% vs 23%)
- Craving (-10 vs +0.7)

*No Black Box LFTs Warning Label for IM formulation
**Opioid Agonist Therapy (Methadone and Buprenorphine)**

- **Acute use**
  - Normal Euphoria
  - Withdrawal
  - Tolerance & Physical Dependence

- **Chronic use**

**Methadone Hydrochloride**

- Full opioid agonist
- Oral - 80-90% oral bioavailability
- Tablets, Liquid Solution, Parenteral (50%)
- PO onset of action 30-60 minutes
- Duration of action
  - 24-36 hours to treat opioid use disorders (OUD)
  - 6-8 hours to treat pain
- Proper dosing for OUD
  - 20-40 mg for acute withdrawal
  - > 80 mg for craving, "opioid blockade"

**Methadone Maintenance Treatment**

- Highly regulated - Narcotic Addict Treatment Act 1974
- Created Opioid Treatment Programs (OTPs)
- Separate system not involving primary care or pharmacists
- Treatment (methadone dispensing) for opioid use disorder limited to licensed OTPs
- It is illegal for a physician to prescribe methadone for the treatment of opioid use disorders in an office-based practice

**Methadone Maintenance in OTP**

- **Highly Structured**
  - Daily nursing assessment
  - Weekly individual and/or group counseling
  - Random supervised drug testing
  - Psychiatric services
  - Medical services
  - Methadone dosing
  - Observed daily ⇒ "Take homes" based on stability and time in treatment. Max: 27 take homes. Varies by state, county and individual clinics

**Methadone Maintenance Treatment Benefits**

- Increases overall survival
- Increases treatment retention
- Decreases illicit opioid use
- Decreases hepatitis and HIV seroconversion
- Decreases criminal activity
- Increases employment
- Improves birth outcomes

**Methadone Maintenance Treatment Limitations**

- Limited access
- Inconvenient and highly punitive
- Mixes stable and unstable patients
- Lack of privacy
- No ability to "graduate" from program
- Stigma
### Buprenorphine
- Partial mu-opioid agonist
- Schedule III
- Metabolism: In liver with N-dealkylation by cytochrome P450 3A4 enzyme system into an active metabolite norbuprenorphine
- Norbuprenorphine undergoes further glucuronidation
- Elimination: Excreted in feces (70%) and urine (30%)
- Mean elimination half-life = 37 hours
- Commercial screening urine drug test for parent compound and metabolite
- Does NOT show as opiate positive on standard screen

### Purpose of Naloxone in “combo”
- Naloxone has limited bio-availability orally or sublingually, but is active parenterally, e.g., injected SQ, IM or IV
- The combo product, if crushed, dissolved and injected the:
  - naloxone may cause initial withdrawal if the person is opioid physically dependent.
  - decreasing diversion and misuse
  - naloxone will block, or attenuate, the opioid agonist effect of the buprenorphine
  - therefore safer if diverted


### Buprenorphine Formulations
- Approved for moderate to severe OUDs, can be used OFF LABEL for pain
- Sublingual forms (tablets and films)
  - “Combo” (buprenorphine/naloxone)
  - “Mono” (buprenorphine only)
- Approved for pain and NOT OUDs
- Parenteral form
- Transdermal Patch (7-day)

### Buprenorphine/Naloxone Bioavailability
- If dissolved sublingually
  - Buprenorphine is active
  - Naloxone is not active
- If swallowed
  - Buprenorphine not active (minimal oral bioavailability)
  - Naloxone not active
- If injected
  - Buprenorphine active, but
  - Naloxone active x 20 minutes so attenuates the parenteral “rush”
- Not time released so tablets/film strip can be split

### Buprenorphine Efficacy Summary
- Studies (RCT) show buprenorphine more effective than placebo and equally effective to moderate doses (80 mg) of methadone on primary outcomes of:
  - Abstinence from illicit opioid use
  - Retention in treatment
  - Decreased opioid craving

- Johnson et al. NEJM. 2000.
- Fudala Pi et al. NEJM. 2005.

### Overdose Risk Minimal
- Low risk of clinically significant problems
- Pre-clinical studies suggest high doses of buprenorphine should not produce respiratory depression or other significant problems
- No reports of respiratory depression in clinical trials
- Overdose and misuse (e.g., injecting) of buprenorphine combined with other CNS depressants (e.g., respiratory depression and over dose death)
- France; IV buprenorphine + high potency benzodiazepines = deaths
**Buprenorphine Safety**

- Highly safe medication
  - for both acute and chronic dosing
- Primary side effects:
  - nausea and constipation
  - like other mu agonist opioids, but may be less severe and more self-limiting
- No evidence of significant disruption in cognitive or psychomotor performance with buprenorphine maintenance
- No evidence of organ damage with chronic dosing of Buprenorphine "mono" or "combo"

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**LFTs with Sublingual Buprenorphine**

<table>
<thead>
<tr>
<th>AST and ALT</th>
<th>Buprenorphine/naloxone (mean %)</th>
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<tbody>
<tr>
<td>Baseline ≤2x ULN remained ≤2x ULN</td>
<td>273 (80.3)</td>
</tr>
<tr>
<td>Baseline ≤2x ULN then increased &gt;2x ULN</td>
<td>43 (12.6)</td>
</tr>
<tr>
<td>Baseline &gt;2x ULN then decreased and remained ≤2x ULN</td>
<td>11 (2.9)</td>
</tr>
<tr>
<td>Baseline &gt;2x ULN not decrease ≤2x ULN or increase &gt;2x baseline value</td>
<td>1 (0.3)</td>
</tr>
<tr>
<td>Baseline &gt;2x ULN then increased &gt;2x baseline value</td>
<td>9 (2.6)</td>
</tr>
</tbody>
</table>

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**Abuse Potential of Buprenorphine**

- Euphoria in non-opioid dependent individuals
- Abuse potential less than full opioid agonists
- Abuse among opioid-dependent individuals is relatively low
- Combination product theoretically less likely to be abused by IV route
- Most illicit use is to prevent or treat withdrawal and cravings

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Module II Objectives

- This module will cover an overview of implementing Office-Based Opioid Treatment (OBOT) including:
  - Patient assessment
  - Office management
  - Medication management
  - Role of nonpharmacotherapy
  - Patient monitoring
  - Relapse
  - Case discussion: Induction and Stabilization

Assessment Overview

1. Establish diagnosis of opioid use disorder and current opioid use history
2. Document use of alcohol and other drugs and need for medically supervised withdrawal management
3. Identify comorbid medical and psychiatric conditions; how, when, where they will be addressed
4. Screen for and address communicable diseases
5. Evaluate level of physical, psychological and social functioning or impairment
6. Determine patient’s readiness to participate in treatment

Patient Assessment

DSM 5 Opioid Use Disorders

1. Tolerance
2. Withdrawal
3. Loss of Control
   - Larger amounts and/or longer periods
   - Inability to cut down on or control use
   - Increased time spent obtaining, using or recovering
4. Craving/Compulsion
5. Use Despite Negative Consequences
   - 7. Role failure, work, home, school
   - 8. Social, interpersonal problems
   - 9. Reducing social, work, recreational activity
   - 10. Physical hazards
   - 11. Physical or psychological harm

Current opioid use history

- Quantity used per day
- Type: heroin, prescription opioids
- Routes: IV, IM, SC, PO, intranasal, inhaled
- Last used, date and time
- Previous attempts to discontinue
- Past treatment experience
  - Nonpharmacologic
  - Pharmacologic with agonist (methadone, buprenorphine) and antagonist (naltrexone) therapies

Mild (1-3), moderate (4-5), severe (≥6)

Not valid if opioid taken as prescribed
**Screening for Alcohol and Other Substance Use**

**Alcohol**
“Do you sometimes drink beer, wine or other alcoholic beverages?”

“How many times in the past year have you had 5 (4 for women) or more drinks in a day?”
(positive: > never)

**Drugs**
“How many times in the past year have you used an illegal drug or used a prescription medication for non-medical reasons?”
(positive: > never)

**Concurrent sedative-hypnotics?**
Alcohol and other sedative-hypnotics are relative contraindications to buprenorphine
- Deaths have resulted from injecting buprenorphine and benzodiazepines
- Avoid alcohol while taking buprenorphine to avoid overdose

Identify and refer patients who are willing and able to undergo medically supervised withdrawal management from alcohol, benzodiazepines, or other sedatives

Fishman et al. 2005; McNicholas, 2008; Larie et al. 2003.

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**Co-morbidity?**

- Medical
  - Past and present medical illnesses, hospitalizations, surgeries, accidents/injuries
  - Current medications, drug allergies
  - Is the patient taking other medications that may interact with buprenorphine, e.g., opioids, naltrexone, sedative-hypnotics?

- Psychiatric
  - History of inpatient and/or outpatient treatment
  - Is the patient psychologically stable?
  - Are the psychosocial circumstances of the patient stable and supportive?

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**Physical Examination**

- Standard physical examination
  - Pay attention to:
    - Stigmata of injection drug use, e.g., needle tracks, skin and soft tissue infections
    - Stigmata of chronic infections, e.g., HIV, hepatitis C
    - Neurocognitive function
    - Liver disease and dysfunction

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**Laboratory Evaluation**

- Liver function tests
- Hepatitis and HIV serologies
- Pregnancy test for women
- Urine drug testing
  - Naturally occurring opiates (morphine, heroin), codeine
  - Synthetic and semisynthetic opioids (methadone, oxycodone)
  - Other commonly used drugs (cocaine, amphetamines, benzodiazepines)

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**Is patient ready to participate in treatment?**

- Patient understands the risks and benefits of (and alternatives to) buprenorphine treatment
- Patient expects to follow safety procedures
- Demonstrates indicators of reliability, e.g., steady employment, adherence to other medications and appointments?
Are you ready to treat your patient?
- Are there resources available in the office to provide appropriate treatment? Medical or psychiatric care?
- On-call coverage?
- Are there treatment programs available that will accept referral for more intensive levels of service if needed?

Words of wisdom
- Don't start with the most complicated
- Start with 1, not 30
- Know your limits
- Don't be afraid to consult and refer

Office Management

Before getting started...
- Make treatment goals and expectations clear to patient
- Know community referral sources to expedite referral when a patient needs more than your practice can offer
- Check state Prescription Drug Monitoring Program (PDMP) to verify patient medication history
- Check urine drug test to confirm patient substance use history
- Use a Treatment Agreement that includes a plan of care (e.g., medication management, monitoring) and informed consent (e.g., adverse effects)

Medical Records Confidentiality
- Specific federal and state regulations govern disclosure of a patient's identity and treatment information
- Confidentiality Statutes relevant to treatment of SUDs:
  - Title 42, Part 2, Code of Federal Regulations (42 CFR Part 2)
    - The logic behind these regulations is that persons with SUDs are more likely to seek and succeed at treatment if they know their need for treatment will not be disclosed unnecessarily
    - Knowledge of these statutes is important for those providing SUD treatment as the rules may apply to their practice

Billing for OBOT
- OBOT is standard medical care: billing procedures are standard
- The ICD-9 Code for opioid dependence is 304.0x.
  - The fifth (x) digit sub-classifications are: 0=unspecified, 1=continuous, 2=episodic, 3=in remission
- Physicians billing codes: (CPT) billing codes, accepted by all payers
- No specific Addiction Medicine codes. Same codes as other ambulatory care services

DEA Inspection
- DEA is mandated to protect the public's safety
- DEA is required to ensure that DEA Registrants comply with the Controlled Substance Act and its implementing regulations
  - Inspections (Unannounced) of buprenorphine waivered physicians maintains the integrity of the inspection process
  - Audit of dispensing records to ensure accountability
  - Verify patient limit (30, 100) compliance
Clinical Uses of Buprenorphine

- Induction
- Stabilization/Maintenance
- Tapering off Maintenance (Discontinuation)
- Buprenorphine for Opioid “Detoxification”

Buprenorphine Induction:
Patient Instructions
- Come in in mild to moderate withdrawal
- Don’t plan to drive home
- Plan to be at clinic or office for up to 3 hours (may bring a sandwich, book, etc.)
- Ready to give urine sample
- Bring medication bottle, or have it delivered if applicable (prescribe vs. dispense)
- Accompanied by significant other, if possible

COWS: Clinical Opioid Withdrawal Scale

Wesson DR et al. J Psychoactive Drugs. 2003

Buprenorphine Induction
Overall Goals
- To find the dose of buprenorphine at which the patient:
  - Has no opioid withdrawal symptoms
  - Discontinues or markedly reduces use of other opioids
  - Experiences decreased cravings
  - Has minimal/no side effects

Buprenorphine Induction
Practical Issues
- Options:
  - Keep a supply of medication in the office for induction administration
  - Must keep the records required by federal and state law for maintaining supplies of controlled substances for administration or dispensing
  - Those records may be audited by the DEA
  - Have the patient fill a prescription for the first day’s dose and bring medication to the office for administration
  - Fax prescription to pharmacy then have it delivered
  - Unobserved “home” induction
  - Advantages and disadvantages to each approach
Numerous studies demonstrate that unobserved “home” inductions are both effective and safe. Should be performed in properly selected patients. Providers and patient/significant other should be able to communicate during the induction. Same protocol as in office-based induction.

Unobserved “Home” Inductions

- Numerous studies demonstrate that unobserved “home” inductions are both effective and safe.
- Should be performed in properly selected patients.
- Providers and patient/significant other should be able to communicate during the induction.
- Same protocol as in office-based induction.

**Buprenorphine: “The First Prescription”**

- The amount of buprenorphine prescribed for induction and stabilization depends on many factors:
  - How reliable is the patient?
  - Is there a significant other who can secure and dispense the medication: particularly important with younger patients
  - How are co-pays managed? Is it reasonable to fill prescriptions every few days?
  - Prior authorizations

**Induction – Day 1**

- Not currently dependent on opioids
  - Uncommon
  - Can still meet DSM-5 criteria
  - No precipitated withdrawal concerns
  - Start low (2 mg), and go slow to avoid opioid side effects
  - Patients are very good at titrating buprenorphine
  - Give them general parameters

**Induction – Day 1**

- Dependent on short-acting opioids
  - Instruct patients to abstain from any opioid use for 12-24 hours (so they are in mild withdrawal at time of first buprenorphine dose)

**Induction – Day 1**

- Dependent on short-acting opioids
  - If patient is not in opioid withdrawal at time of arrival in office:
    - Assess time of last use and consider either:
      - Having him/her return another day
      - Waiting in the office until evidence of withdrawal is seen
      - Or leaving office and returning later in day (with strict instructions to not take opioids while away from the office)
Induction – Day 1
Dependent on short-acting opioids
- First dose: 2/0.5-4/1 mg SL buprenorphine/naloxone
- Monitor in office for 1-3 hrs after first dose and each subsequent dose
- Relief of opioid withdrawal should begin within 30-45 minutes
- Period of greatest severity of buprenorphine-related precipitated withdrawal occurs in the first few hours (1-4 hours) after a dose

Induction – Day 1
Dependent on short-acting opioids
- The length of time the patient is monitored in the office varies depending upon:
  - The clinician's familiarity with the patient
  - The clinician's familiarity with using buprenorphine
  - The patient's level of support at home

Induction – Day 1
Dependent on short-acting opioids
- Can re-dose if needed (every 1-2 hours, if opioid withdrawal subsides then reappears)
- Maximum first day dose of buprenorphine/naloxone= 8mg----16mg
- Dose equivalent of other formulations; e.g. 5.7—11.4 mg of branded SL tablets

Induction – Day 1
Dependent on long-acting opioids
- Recommendations vary about optimal dose of long-acting opioid for transfer (TIP 40 states <30 mg/d methadone)
- More recent clinical experience suggests patients should have dose decreases until they are down to <40 mg/d of methadone or the equivalent
- Begin induction at least 48-72 hours after last dose of methadone, and 36 hours after last dose of sustained release oxycodone (or longer)
- Patient should be in mild to moderate withdrawal at time of first buprenorphine dose
- Use similar induction procedures to "dependent on short-acting opioids"

Induction – Day 1
Managing Precipitated Withdrawal
- If a patient has precipitated withdrawal consider:
  - Giving another dose of buprenorphine, attempting to provide enough agonist effect from buprenorphine to suppress the withdrawal
  - Stopping the induction, provide symptomatic treatments for the withdrawal symptoms, and have patient return the next day
- Since the latter would risk loss of the patient, the first option should be considered

Stabilization/Maintenance
- On 2nd day, be in contact with patient (in office, via phone, etc.)
- Adjust dose accordingly based on patient's experiences on first day
- Continue adjusting dose by 2/0.5-4/1 mg increments until an initial target dose of 8/2—16/4 mg is achieved during the induction phase
- Generally 24mg of buprenorphine is considered a maximal dose, but some patients may require a higher dose
After the first day of buprenorphine, induction for patients who are dependent on either short-acting or long-acting opioids, the procedures are essentially the same.

- Adjust dose according to the patient’s experiences:
  - Lower dose if patient was over-medicated at end of Day 1
  - Higher dose if there were withdrawal symptoms after leaving your office and/or if patient used opioid agonists.
  - Don’t assume abstinence after the first day’s dose.

**Stabilization/Maintenance**

- The patient should receive a daily dose until stabilized.
- Patient should be dosed once daily or twice daily, but not more frequently than twice daily.
- Multiple daily doses which mimic addictive behavior is not recommended.
- An exception daily dosing (e.g., mg qid) is indicated if concurrent opioid use disorder and pain are being treated.

**Stabilization/Maintenance**

- Once stabilized, the patient can be shifted to alternate day dosing (e.g., every other day, MWF, or every third day, MTh).
- Increase dose on dosing day by amount not received on other days (e.g., if on 8 mg/d, switch to 16/16/24 mg MWF).
- Non-daily dosing is most appropriate if the patient is receiving observed dosing in an OTP.
- For OBOT patients daily dosing is the norm.

**How Long Should Buprenorphine Maintenance Continue?**

- No data to provide guidance on how long to treat a patient with buprenorphine/naloxone maintenance.
- Studies as long as 16 weeks show high relapse rates with medical withdrawal (Weiss et al., 2011).
- Patients can be retained long term; showed approximately 75% retention at one year with maintenance (Kakko et al., 2003).
- Continue maintenance as long as patient is benefiting from treatment (opioid/other drug use, employment, educational goals pursued, improvement in relationships, improvement in medical/mental illnesses, engaged in psychosocial treatment).

**Buprenorphine Discontinuation**

- First question is why?
- Many studies show high relapse rates with tapers and withdrawal from maintenance agonist.
- Some studies show normalization of brain function with maintenance.
- Comprehensive discussion with patient and significant others to explore reasons for discontinuation.

**Buprenorphine Dosing**

- > 24 mg/day (Full Review: medical/behavioral)
- > 16–24 mg/day (Consider: Patient Difference)
- ≤ 16 mg/day (typical)


Kakko et al., 2003.
Buprenorphine Discontinuation
- Patients should continue to be followed by provider after discontinuation
- Naltrexone therapy should be considered
- Psychosocial treatments should continue
- Patients should be told they can resume buprenorphine treatment if cravings, lapses, or relapses occur

Medically Supervised Withdrawal “Detox” using Buprenorphine
- Conflicting data on outcomes comparing shorter versus longer duration of tapering
- Regardless of the buprenorphine withdrawal duration consider use of ancillary medications to assist with symptoms of opioid withdrawal (e.g., medications for arthralgias, nausea, insomnia)

Medically Supervised Withdrawal “Detox” using Buprenorphine
Rapid ≤ 3 days
- Reports show buprenorphine suppresses opioid withdrawal signs and symptoms (better than clonidine)
- Using sublingual tablets:
  - First day: 8/2-12/3 mg sl
  - Second day: 8/2-12/3 mg sl
  - Third (last) day: 6/1.5 mg sl

Medically Supervised Withdrawal “Detox” using Buprenorphine
30 days*

<table>
<thead>
<tr>
<th>Study Day</th>
<th>Buprenorphine-Naloxone Dose mg</th>
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<tr>
<td>1</td>
<td>14+4 as needed</td>
</tr>
<tr>
<td>2</td>
<td>10</td>
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<tr>
<td>3</td>
<td>8</td>
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<td>8</td>
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</tr>
<tr>
<td>9</td>
<td>2</td>
</tr>
<tr>
<td>10</td>
<td>2</td>
</tr>
</tbody>
</table>

Withdrawal over 4-30 days is common in clinical practice. Buprenorphine is very flexible and withdrawal can be achieved rapidly or slowly, depending on treatment issues.

*Protocol Developed by NIDA Clinical Trials Network

Opioid Use Disorder (OUD): Behavioral Treatment Components
- Psychosocial Services: often helpful for treatment of OUD
- Can be delivered directly by physician and/or by referral when needed
- DATA 2000: “...the practitioner has the capacity to refer the patients for appropriate counseling and other appropriate ancillary services.”
- Refer patient as clinically determined to:
  - Individual and group therapy
  - Family therapy
  - 12 Step
  - Higher psychiatric severity patients more responsive to increased services

Role of Non-Pharmacological Treatment
Is Behavioral Treatment in OBOT Effective?

- Three trials show that additional behavioral therapy (i.e., CBT, drug counseling) does NOT significantly improve outcomes over that achieved by buprenorphine PLUS medical management or “medical counseling”

Primary Care Medical Management Critical Elements

- Provision of buprenorphine maintenance
- Monitoring of compliance with buprenorphine maintenance
- Monitoring of patients’ drug use, symptoms, and progress
- Education regarding opioid use disorder and buprenorphine maintenance treatment
- Encouragement to achieve abstinence from illicit opioids and to adhere to all treatment recommendations
- Encouragement to attend self-help groups
- Provision of brief advice modeled on the education provided in standard drug counseling, such as encouraging patients to make lifestyle changes that support recovery, and to avoid potential triggers of drug use
- Identification and treatment of medical complications of opioid use
- Referrals to specialty services in the community (e.g., vocational, legal, housing or social services) if necessary

Patient Management, Monitoring

- Discuss and document specific goals
- Set specific time periods
- Document progress on goals at each visit
- Examples:
  - Achieve abstinence from illicit and non-prescribed drugs
  - Meet with clinician
  - Attend meetings
  - Job applications

Follow-up Visits

- Face to face visits to check safety, adherence
- Initial Frequency: every 1-2 weeks until stable
- Monthly once stabilized
- Check dosing, intervals, sublingual technique
- Safety issues: Side effects, safe storage

Follow-up Visits

- Withdrawal/craving/triggers
- Tobacco, alcohol, and other drug use
- Urine drug tests (UDT) and pill counts
  - Frequency varies with treatment stage
  - Prescription drug monitoring program (PDMP)
Follow-up Visits
- Confirm behavioral treatment
- 12 step facilitation
- Medical problems & symptoms
- Psychiatric problems & symptoms
- Outside medications and providers
- Housing
- Employment
- Family/Relationships
- Legal issues...

Urine Drug Testing (UDT)
- Objective information
  - Evidence of therapeutic adherence
  - Evidence of use or non-use of illicit drugs
  - Monitoring of treatment progress and safety
  - Reinforces success with treatment
  - Part of standard of care
  - Identify those who may need higher level of care

UDT: Frequency
- SAMHSA TIP 40 2004
- At least monthly
- More frequently early in treatment (every 1-2 weeks)
- Vary among states, insurers
- Urine is preferred medium for testing due to
  - Ease of obtaining sample
  - Presence, persistence of metabolites
  - Lowest cost
  - Availability of office-based testing tools

UDT: Implementation
- Discuss with patient
  - This is for safety and is the standard of care
  - Know scope and limits of tests and lab
  - Beware false negatives and positives
  - Consider random versus scheduled testing
  - Incorporate quality control procedures
  - Consider establishing consult lab linkage
    - GCMS/LCMS confirmatory testing
    - Expert consultation on test interpretation
    - Online reporting of results
    - Onsite and/or observed testing when needed

UDT: Immunoassays
- PROS:
  - Point of care, or lab based
  - Fast
  - Easy
  - Cheap
  - Specific tests available for many drugs
  - Oxycodone
  - Buprenorphine
  - Can be used as screening with option for confirmation

- CONS:
  - Qualitative tests
  - Cutoff ng/ml
  - Opiates 300
  - Cocaine metabolite 300
  - False positives
  - Cross-reactivity
  - Contamination
  - No non-morphine opioids
  - Unless specifically tested
  - No non-oxazepam benzos
  - Unless specifically tested

UDT: Detection Windows in Urine

<table>
<thead>
<tr>
<th>Drug/Medication</th>
<th>Primary Metabolite</th>
<th>Ave. Detection Time (days)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Opiates (heroin, morphine)</td>
<td>Morphine</td>
<td>2-3</td>
</tr>
<tr>
<td>Semisynthetic Opioids (oxycodone, hydrocodone)</td>
<td>Variable</td>
<td>2-3</td>
</tr>
<tr>
<td>Methadone</td>
<td>EDDP</td>
<td>2-3</td>
</tr>
<tr>
<td>Buprenorphine</td>
<td>Non-buprenorphine</td>
<td>2-3</td>
</tr>
<tr>
<td>Cocaine</td>
<td>benzoylecgonine</td>
<td>2-3</td>
</tr>
<tr>
<td>Amphetamines</td>
<td></td>
<td>2-3</td>
</tr>
<tr>
<td>Benzodiazepine</td>
<td>Varies by medication type</td>
<td>Variable with half life unreliable immunoassays</td>
</tr>
<tr>
<td>Marijuana Occasional</td>
<td>THC</td>
<td>Up to 30</td>
</tr>
<tr>
<td>Marijuana Chronic</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
**UDT: GCMS/LCMS**
- Gas or liquid chromatography, mass spectrometry
- Identifies specific drugs/levels
- Limitations:
  - Very costly: $200-$800 per “panel”
  - Requires specialized lab
  - Levels do not indicate amount of medication taken!
  - Variables: time of dosing, metabolism, GFR, hydration
  - Very sensitive: minor metabolites confusing

**UDT: Opioid Metabolism**

**Pill Counts**
- Objective information
  - Confirm medication adherence
  - Minimize diversion
  - Frequency varies with patient progress
  - Best option when diversion suspected
  - Patient brings in medication supply
  - Confirm patient ID and fill date on bottle/box
  - Have patient count them in front of staff member
  - All tablets should be identical
  - Amount should match expected quantity

**Prescription Drug Monitoring Program (PDMP)**
- State-wide system tracking prescriptions
  - Decreasing or preventing misuse of medications
  - Improving clinical decision making
  - Pharmacies report information to state
  - Information varies:
    - Schedule II, II and III, II-IV, II-V
    - Some selected non-scheduled medications with abuse potential: carisoprodol, tramadol
  - Data availability
    - Format/eligibility vary by state

**Relapse: Prevention and Management**
- Relapse is a process in which return to substance use results from maladaptive responses to stressors and stimuli
- Relapse precipitants
  - Negative affect (anger, fatigue, boredom, family conflict)
  - Cravings/cues (people, places and things)
  - Social pressure (social functions)
  - Education patients about how to anticipate/avoid/cope with these precipitants
  - After initial use (a lapse), patients may experience guilt, shame resulting in return to heavy use
  - Recovery is a learning process, lapses provide valuable lessons
  - Return to substance use requires prompt evaluation and possible referral to additional or higher level of care


Doyle TF, Friedmann PD, Zywiak WH. Addressing Unhealthy Alcohol Use in Primary Care, 2013.

**PDMP: Limitations**
- Not all prescriptions tracked (Veteran’s Admin)
- Methadone and buprenorphine from OTP’s NOT INCLUDED
- Not all data readily available to providers
- Lack of communication between all state programs
- Time needed to access reports
- Limitations in who can access reports
- Restrictions on access? (the VA example)
Mother calls your office seeking treatment for her daughter, Paula, who is addicted to heroin

- Paula is a 23 yo female, graduate student in social work
- She is agreeable to having her mother come in for the consultation and evaluation
- She is comfortable and not in opioid withdrawal during the initial consultation

- She continued requesting oxycodone refills even though her pain had resolved.
- When the orthopedist refused to continue prescribing oxycodone she started buying them from friends increasing to ~200mg daily.
- A year ago she entered a 28 day abstinence-based rehab, never followed up in after care, relapsed 6 weeks later.
- Due to cost and availability she switched from oxycodone to sniffing heroin ~10 bags daily—Last use 4 hours ago.
- Patient agrees to have mother present to discuss treatment options.

You take a history from Paula while her mother sits in the waiting room.
- She relates feeling anxious most of her life.
- She started smoking marijuana and drinking alcohol on the weekends in high school.
- In college she fractured her ankle playing basketball, and was treated with oxycodone. She noticed that in addition to pain control, her anxiety decreased, and she reported feeling “normal” and “peaceful.”

You present the options of opioid agonist maintenance therapy (methadone, buprenorphine), antagonist maintenance with naltrexone, and another attempt at “detox” and medication-free treatment.

Paula and her mother have done their research, Paula has a friend doing well on buprenorphine, and they decide on buprenorphine.
- They understand that some form of counseling will also be a part of the treatment plan.
- Paula has insurance, so access is not a problem.
Case Questions

- Is Paula ready for buprenorphine induction at this time? If not, how will you decide when she is ready?
- Is the patient a candidate for unobserved "home" induction?

You explain that since Paula is physically dependent on opioids, she must be in mild-moderate spontaneous withdrawal, to avoid precipitated withdrawal. She has done her homework, and understands the issue.

You tell her to discontinue all opioids for at least 12 hours. She has decided on doing the induction the next morning.

She returns the next day with her mother. She is visibly uncomfortable, and has a COWS score of 12.

- Is she ready for the induction?

You instruct her that buprenorphine/naloxone is always administered sublingually or via the buccal mucosa—never swallowed whole.

- She is instructed on the proper administration procedures to maximize buprenorphine bioavailability.

You give her buprenorphine 4/1 mg.

- How long to initial effect?
- How long to peak effect?
- After her initial dose you give her another 4/1 mg for continue withdrawal.

- When can the patient leave the office?
- Can she take more buprenorphine after leaving the office?
- When should she contact you?

- Should the stabilization dose be divided or taken once per day?
- How often should stabilization doses be increased?
- Once dose stabilization occurs, are maintenance dose increases due to tolerance common? Or are lower doses required over time?

Paula remained on buprenorphine/naloxone 16/4 mg per day for the next 6 months and had no relapses.

- She was adherent with weekly counseling and office monitoring including urine drug tests and pill counts.
- There were no concerning behaviors on the PDMP.
How long should Paula be maintained on the buprenorphine?

How will you decide if and when she is ready to be tapered?

How would you taper her off buprenorphine?
Module III
Special Populations

Adolescents and Young Adults

In this module we will review...
- Adolescents and young adults
- Pregnancy, neonatal abstinence and breastfeeding
- Medical co-morbidities
- Psychiatric co-morbidities
- Managing pain

Use of Pharmacologic Treatment with Adolescents
- Pharmacologic therapy is recommended for all adolescents with severe opioid use disorder
- Buprenorphine is considered first line treatment
  - Most methadone clinics cannot admit patients under 18 years old, though methadone may be a good option for young adults with unstable living arrangements as daily visits provide structure and eliminate the need to manage medications at home
  - Naltrexone is also an option for adolescents and also may be clinically useful for adolescents young adults living away from home, or patients with co-occurring alcohol use disorders

Treatment Duration
- The optimal length of time for medication treatment is not known
  - Studies in adults have found that patients continued to improve over the course of the first 6 years of treatment
  - However, the impact of exposure to long term agonists/antagonists on the developing brain are unknown
  - Avoid changing medications during periods of stress – final exams, summer vacation, high school graduation, etc.
  - Patients who discontinue medications should continue in counseling and should be monitored closely for relapse for an extended period of time

Confidentiality
Teens Presenting with Parents
- In many cases, adolescents will present for treatment with the knowledge, and often with the support, of parents
  - Parents are often the first ones teens turn to for help
- In these cases, managing confidentiality is a clinical decision of what information to share with parents in the context of parents already being aware of the “big picture.” In these cases,
  - Share clinical impressions and treatment recommendations
  - Involve parents if a teen's behavior puts him/her in acute danger
  - Avoid sharing details that are not directly relevant to treatment
  - Parents have access to medical records and may seek information if they desire
Confidentiality
Parental Request to See Their Child's Chart
- In some settings, the parent of a minor may have the right to see the chart. Check with a legal expert.
- If the parent does have the right, discuss the pros and cons.

<table>
<thead>
<tr>
<th>PROS</th>
<th>CONS</th>
</tr>
</thead>
<tbody>
<tr>
<td>May obtain vital health information about patient.</td>
<td>May reveal previous drug use information to share other information in the future.</td>
</tr>
<tr>
<td>May damage the therapeutic relationship between provider and teen.</td>
<td>Teen may stop out of treatment.</td>
</tr>
<tr>
<td>Chart may not contain information sought.</td>
<td></td>
</tr>
</tbody>
</table>

- If parents insist on viewing chart, have them make a formal medical records request.

Confidentiality
Managing Teens that Refuse to Involve Parents
- Ask adolescent their reasons for excluding parents. Many teens could benefit from the support of parents, but are too embarrassed to discuss the problem.
- In these cases, offer to treat confidentially and leave the decision of how to proceed up to the teen.
- Review the difficulty in keeping information confidential.
- Remind teens that you cannot/will not lie to parents.
- Discuss what will happen if parents request to speak with you or see medical records.
- Ask what would happen if a parent learned about a drug problem by accident.
- Offer to help "break the news" to parents.
- Emphasize that teens who enter treatment should be proud of their decision to get help.

Confidentiality
Managing Teens Who Refuse to Involve Parents
- If the teen fears that revealing a SUD would put him/her at risk of abuse, or if teen decides not to involve parents, proceed with confidential treatment.
- Seek legal expertise to ensure that "mature minor" or "emancipated" status will allow you to treat an adolescent for a substance use disorder without consent in your state.
- Review plans for keeping treatment secretive; ask the teen how likely his/her plan is to succeed.
- Discuss issues of confidentiality with the rest of the treatment team (counselors, psychiatrists or other professionals).
- Ensure all documentation is in place for treating an adolescents as an "emancipated" or "mature" minor.

Confidentiality
Tips on "Breaking News" to Parents
- If an adolescent asks for help in disclosing a SUD.
  - Choose words that are acceptable to the teen and convey the message accurately. "Pain meds" may be preferable to "narcotics".
  - Share diagnosis and treatment plan; avoid details from the history.
  - Support self-efficacy by congratulating the teen on recognizing his/her problem and seeking help.
- Support parents who may be shocked and disappointed.
  - Focus on the positive: treatment-seeking behavior.
  - Reassure that you can help.
  - Redirect if a parent becomes very angry or invasive.
  - If necessary, ask everyone to calm down before leaving the office.

Pregnancy Neonatal Abstinence Breastfeeding
Pregnancy: Initial Evaluation

- Know about specialized treatment services available in the community for pregnant, opioid-dependent patients.
- Referral should be made regardless of the patient's decision to continue the pregnancy.
- Evaluate for intrauterine pregnancy, rule out ectopic or abnormal pregnancy immediately.
- Obtain consent to talk to her obstetric provider.
- Educate and obtain informed consent for opioid agonist therapy prior to induction.

Pregnancy: Benefits of Opioid Agonist Therapy

**Maternal Benefits**
- 70% reduction in overdose related deaths
- Decrease in risk of HIV, HBV, HCV
- Increased engagement in prenatal care and recovery treatment

**Fetal Benefits**
- Reduces fluctuations in maternal opioid levels; reducing fetal stress
- Decrease in intrauterine fetal demise
- Decrease in intrauterine growth restriction
- Decrease in preterm delivery

Should women undergo Detoxification in pregnancy?

- Initial studies from 1970s demonstrated fetal distress and 5 fold increase in stillbirth rates with antepartum detoxification (Casper et al. 1972, Zuspan et al. 1974).
- More recent data shows 2nd trimester detoxification can be safe for the fetus however maternal relapse rates prior to delivery range from 70-98% (Luty et al. 2005, Maas et al. 1999, Dahe et al. 1998).
- Maintenance therapy in pregnancy has been shown to increase retention in prenatal care, addiction recovery and in-hospital deliveries (Jones et al. 2008).

Pregnancy: Maintenance Therapy Remains the Standard of Care

- Methadone and buprenorphine (both category C) are safe and effective treatment options in pregnancy.
- The decision of which therapy to start is complex and should be individualized for each woman.
- Based on available options, patient preference, patients' previous treatment experiences, disease severity, social supports, and intensity of treatment needed.

Jones et al. 2010.

Pregnant Physiology

**Changes in Physiology**
- Total blood volume:
- 45% increase by 28wks.
- Cardiac Function:
- 50-55% increase in cardiac output by 2nd trimester.
- GFR doubles.

**Changes in drug metabolism**
- Total body clearance increases.
- Terminal half-life decreases in 2nd and 3rd trimesters.
- Lower trough levels.
- All of which can lead to withdrawal symptoms with increasing gestational age.

Management of Buprenorphine Patient: Newly Pregnant

- For women stable on buprenorphine/naloxone who become pregnant:
- Current standard of care is to switch to buprenorphine monotherapy at the same dose.
- Buprenorphine's current safety profile in pregnancy has been established using the monotherapy.
- The combination therapy has been avoided due to the unknown exposure risk of naloxone in pregnancy (although pregnancy category B) and concern for misuse causing acute withdrawal and fetal distress.
- Preliminary data on the safety of buprenorphine/naloxone use compared to methadone in pregnancy published in 2015.

Wiggland SL et al. 2015.
**Maintenance Therapy in Pregnancy: Neonatal Abstinence Syndrome (NAS)**

- Generalized disorder with dysfunction of the autonomic nervous system, GI tract and respiratory system
- Occurs in 60-80% of infants with intratne exposure to opioid maintenance therapy
- Onset: majority present within 72 hours after delivery
- Duration: up to 4 weeks (prolonged if exposed in utero to more than one substance associated with NAS)
- Treatment:
  - Pharmacologic: DTO, oral morphine, methadone
  - Non-Pharmacologic: breastfeeding, skin-to-skin, swaddling, low stimulation environment, maternal rooming-in

**Breastfeeding Benefits in General Population**

- Benefits for all mother-infant pairs:
  - Decreased risk of SIDS, diabetes, and obesity for children
  - Decreases risk of breast and ovarian cancer for women
  - Improved infant cognitive development
  - Improved mother-infant bonding
  - Financial benefits
- Additional benefits for preterm infants:
  - 50% reduction in necrotizing enterocolitis
  - Better feeding tolerance and attainment of full enteral feedings
  - Decreased rates of late onset sepsis
  - Improved developmental outcomes

**Maternal Dose and NAS Severity**

- No correlation between maternal opioid maintenance therapy dose and the duration or severity of NAS
- Women should be encouraged to report any symptoms of withdrawal through her pregnancy without fear a dose increase will affect her baby's hospital stay or need for NAS treatment

**Opioid Use Disorder and Breastfeeding**

- The transfer of methadone and into human milk is minimal
- Concentrations of methadone in breast milk are unrelated to maternal doses and are particularly low in infant plasma, therefore unlikely to cause any adverse effects on the infant
- Buprenorphine has poor oral bioavailability and is also compatible with breastfeeding
- The amount of buprenorphine in human milk is small and unlikely to have negative effects on the infant
- Both are considered Category L3

**Breastfeeding and NAS**

- Benefits of breastfeeding for newborns with NAS
  - 30% decrease the development of NAS
  - 50% decrease in neonatal hospital stay
  - Improved mother-infant bonding
  - Positive reinforcement for maternal recovery

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AAP 2012.


Medical Co-Morbidities

- Persons with opioid use disorders frequently have or at risk of other comorbid medical conditions
- Office-based buprenorphine treatment provides an opportunity to combine substance use treatment with medical care

Non-Occupational Post-Exposure Prophylaxis (nPEP)

- HIV: 3-drug ART given <72 hrs after exposure to blood or other potentially infectious body fluids from a known HIV+ or high risk source
- HBV: recombinant vaccine series; HBIG within 7 days of unknown or known HBsAg+ source
- HCV: no PEP, but curative early treatment

Free expert consultation at national PEPLine: (888) 448-4911

Source: www.cdc.gov/mmwr

Hepatitis C virus infection

The silent epidemic

- Most common blood-borne infection in U.S., 3.2 million people; 170 million worldwide
- 70-90% PWID; <30% < age 30
- 40-60% of chronic liver disease
  - >50% of incident hepatocellular carcinoma
  - Leading indication for liver transplantation
  - Annual mortality increased >50%, 1999-2007
  - HCV-related deaths outnumber deaths due to HIV

Recommended Testing Sequence for Identifying Current HCV Infection

Natural history of HCV infection, variability from person to person

HIV Treatment

Today's combination antiretroviral therapy: less toxic, fewer pills, higher genetic barrier to resistance

Goals of HIV care:
- Improve individual health outcomes
- Restore health, prolong life in a manner indistinguishable from uninfected persons
- Lower community viral load and HIV transmission to achieve an "AIDS-free generation"

Clinically significant interactions

<table>
<thead>
<tr>
<th>Antiretroviral Agent</th>
<th>Methadone</th>
<th>Buprenorphine</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nucleoside RTI</td>
<td>↓ZDV AUC</td>
<td>none</td>
</tr>
<tr>
<td>Non-Nucleoside RTI</td>
<td>efavirenz</td>
<td>↓methadone</td>
</tr>
<tr>
<td></td>
<td>ritonavir</td>
<td>↑methadone</td>
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<tr>
<td></td>
<td>lopinavir/ritonavir</td>
<td>↓methadone</td>
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<td></td>
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<tr>
<td></td>
<td>darunavir</td>
<td>↓methadone</td>
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<tr>
<td>Integrase Inhibitors</td>
<td>raltegravir</td>
<td>none</td>
</tr>
<tr>
<td></td>
<td>dolutegravir</td>
<td>unknown</td>
</tr>
</tbody>
</table>

PWID less likely to receive ART

Percentage of HIV providers (n=662) who would defer prescribing ART by CD4+ count and injection drug use status

Opioid agonist treatment as HIV prevention

- Methadone-maintained patients report less needle and syringe sharing
- Methadone-maintained patients are 3-6 times less likely to become HIV positive as compared to out-of-treatment heroin users, including among those who continue to use drugs

Buprenorphine and HIV outcomes

HIV-infected patients treated with office-based bup/nx in the Buprenorphine-HIV Evaluation and Support (BHIVES) national demonstration project:

- Decreased opioid use
- Increased HIV ART use
- Experienced higher quality of HIV care
- Reported better quality of life

Altice, Frederick L. et al. J Acquir Immune Defic Syndr. 2011;56(Suppl):S1a

Psychiatric Co-Morbidities

Substance Induced Psychiatric Disorders

- Patient's history suggests symptoms occur only when he/she is actively using substances
- Symptoms are related to intoxication, withdrawal, or ongoing neurobiologic perturbation from substances
- Onset and/or offset of symptoms are preceded by increases or decreases in substance use
- Goal should be sustained abstinence followed by re-evaluation of symptoms

Induced vs Independent Disorder

- Distinguish between substance-induced disorders versus independent psychiatric disorders
  - Substance-induced: Disorders related to the use of psychoactive substances; typically resolve with sustained abstinence
  - Independent: Disorders which arise during times of abstinence; use of psychoactive substances not the etiology

Substance Independent Psychiatric Disorders

- Earliest psychiatric symptoms often precede onset of substance use disorder
- Patient’s history suggests symptoms occur during periods when not using psychoactive substances
- May also find a family history of the disorder
- Goal of substance use disorder treatment should still be cessation of substance use, but treatment must also address psychiatric symptoms simultaneously

Assess: Depression & Anxiety

- Common for patients with opioid use disorder to report high rates of depressive and anxiety symptoms at time of treatment entry
- Symptoms often resolve within a few days after entry (i.e., substance-induced)
- “Sick and tired of being of being sick and tired”
**Major Depression**

- Epidemiology in opioid use disorder
  - Lifetime rates: 15-50%
  - Current rates: 3-25%

**Anxiety Disorders**

- Epidemiology in opioid use disorder
  - Most common anxiety disorders are Phobias, followed by Generalized Anxiety Disorder
  - Lifetime rates: 8-27%
  - Current rates: 5-17%

**Social Anxiety Disorder**

- Features
  - Fear or anxiety about social situations
  - Fear of being negatively evaluated, humiliated
  - Social situations avoided or endured with anxiety
  - Fear out of proportion to actual threat
  - Fear or avoidance lasts ≥ 6 months
- Epidemiology
  - Occurs in ~ 10% of SUD patients
  - Can make attendance at self-help groups challenging

**Post Traumatic Stress Disorder (PTSD)**

- Features
  - Exposure to actual or threatened death, serious injury or sexual violence
  - Intrusion symptoms:
    - Flashbacks / nightmares
    - Intrusive thoughts / feelings
    - Physiologic reactions
  - Avoidance of trauma associated stimuli
  - Negative alterations in cognitions and mood
  - Alterations in in arousal and reactivity
    - Irritability
    - Reckless or self-destructive behavior
    - Hyper-vigilance
    - Startle Reactions
    - Problems with concentration
    - Sleep disturbance

- Common in both male & female opioid addicted
- exact percentages are undetermined
- Patients rarely volunteer the history
- Suspect in men or women with
- Antisocial Personality Disorder
  or Borderline Personality Disorder
- Sexual Abuse history not uncommon

**General Treatment Principles**

- Patients with opioid use disorder and independent depressive, anxiety, or stress disorders
  - Can respond to medication and/or psychotherapy treatments for depression, anxiety, and PTSD
  - Anxiety disorders and PTSD typically treated with antidepressants
  - Generally avoid use of benzodiazepines
  - Risk of misuse
  - Possibility of interactions with buprenorphine
Buprenorphine and Benzodiazepines:
- Among 34 reported buprenorphine-associated overdoses in France, 31 also had benzodiazepines
- Risks of benzodiazepines
  - Tolerance
  - Withdrawal
  - Excess sedation
  - Falls
  - Cognitive impairment
  - Reinforcement/reward/addiction
- Advantages of benzodiazepines
  - Rapid elimination of anxiety symptoms or insomnia when used short term


Antisocial Personality Disorder
- **Epidemiology**
  - Personality disorders highly prevalent in patients with opioid use disorder
  - Most common is Antisocial Personality Disorder (ASP) particularly in men
  - Rates (any personality disorder): 14-68%
  - Rates (ASP): 14-55%

Management of Personality Disorder Patients
- Distinguish between behaviors that occur as part of drug use lifestyle versus personality disorder
- If needed establish limits and boundaries calmly but firmly
- Recognize limitations to treatment in office based setting
- Refer to specialized services once cessation of illicit substance use is achieved, if patient is distressed

Antisocial Personality Disorder
- **Features**
  - Problems begin in childhood
  - Conduct Disorder
  - Repeatedly breaking the law
  - Lying / conning
  - Impulsivity
  - Physical fights
  - Disregard for safety of self, others
  - Consistent irresponsibility
  - Lack of remorse

Managing Pain

Altered Pain Experience
- In experimental pain studies...
  - Patients with active opioid use disorder have less pain tolerance than peers in remission or matched controls
  - Patients with a h/o opioid use disorder have less pain tolerance than siblings without an addiction history
  - Patients on opioid maintenance treatment (i.e. methadone, buprenorphine) have less pain tolerance than matched controls
- Which came first?
  - Opioid use disorder or less pain tolerance?

Patients with an opioid use disorder who are physically dependent on Opioid Agonist Treatment (i.e., methadone or buprenorphine) must be maintained on a daily equivalence before ANY analgesic effect is realized with opioids used to treat acute pain.

Opioid analgesic requirements are often higher due to increased pain sensitivity and opioid cross tolerance.

Alford, DP; Compton, F; Samet, JH. Ann Intern Med. 2006.

“Opioid Debt”

Buprenorphine as an Analgesic

Parenteral and transdermal formulations approved for pain not addiction treatment

CAN’T be used off-label under Drug Addiction Treatment Act of 2000 (DATA 2000) for addiction

Sublingual formulation approved for addiction not pain treatment

CAN be used off-label for pain

Acute Pain
Buprenorphine Maintenance Treatment

Theoretical Concern

Buprenorphine (a partial mu agonist) may

antagonize the effects of previously administered opioids or

block the effects of subsequent administered opioids

However...Experimental mouse and rat pain models

Combination of buprenorphine and full opioid agonists (morphine, oxycodone, hydromorphone, fentanyl) resulted in additive or synergistic effects

Receptor occupancy by buprenorphine does not appear to cause impairment of mu-opioid receptor accessibility


Acute Pain
Buprenorphine Maintenance Treatment

Options

Continue buprenorphine and titrate short-acting opioid analgesic

Discontinue buprenorphine, use opioid analgesic, then re-induce

Divide buprenorphine to every 6-8 hours

Use supplemental doses of buprenorphine+

If inpatient,

discontinue buprenorphine

start methadone 20-40mg (or other long-acting opioid) for opioid debt

use short-acting opioid analgesics

then re-induce w/buprenorphine when acute pain resolves

Alford, DP; Compton, F; Samet, JH. Ann Intern Med. 2006.
Book, SW; Myrick, H; Malcolm, R; Strain, EC. Am J Psychiatry. 2007.

Chronic Pain
Buprenorphine Maintenance Treatment

Systematic review

10 trials involving 1,190 patients

Due to heterogeneity of studies, pooling results and meta-analysis not possible

All studies reported effectiveness in treating chronic pain

Majority of studies were observational and low quality

Current evidence insufficient to determine effectiveness of SL buprenorphine for treatment of chronic pain

Cotes, J; Montgomery, L. Pain Medicine. 2014.
Robert

- 35-year-old junior high school math teacher
- Using prescription opioids and intranasal heroin on and off since age 22
- Has been through >15 episodes of medically supervised withdrawal (“detoxification”).
- Last treatment included a 28-day residential program during his summer break, and attending daily AA meetings.
- Remained in recovery for 6 months but relapsed 3 months ago and is in some difficulty because of “calling in sick too much.”
- His wife is in recovery, and insisted that he return to treatment after she discovered he was taking oxycodone pills from several doctors for a back injury following an automobile accident. She is unaware that he is also using heroin daily.
- Family history of alcoholism
- He denies alcohol or tobacco use
- His only current medical problem is mild asthma. His back pain has resolved.
- He is hepatitis C and HIV negative.

Robert questions

- Does Robert meet DSM-5 criteria for an opioid use disorder? If so, how?
- What are the treatment options for Robert?
- How would you assess the need for pharmacotherapy (e.g., methadone, buprenorphine, naltrexone) for Robert?

Robert states...

- "Doc, I know I’m an addict. My wife cleaned up when she was pregnant with our daughter, and she just got her 12-year chip. She moved on with her life, but I’m stuck.”
- "My back injury threw me into a tailspin. At first, I really needed the “percs”, but now I’m just using them to “feel normal” and to “prevent withdrawal.” I really need your help. If my wife finds out I’m back on heroin, she’ll leave me this time.”
John
- 28 year-old engineer requesting transfer from his methadone maintenance program to your office-based buprenorphine treatment program
- On methadone maintenance treatment program for 13 years but is tired of all the strict rules and policies
- Current methadone dose is 95 mg
- His 13 day take homes were recently discontinued when he missed his 2nd group counseling session in 3 months. He is now required to have daily observed dosing

John
- He does not think the group counseling was helping him anymore. He thinks it was helpful in the beginning but now it is just a burden
- He is caring for his sick parents along with working full time which makes it difficult for him to reliably attend his weekly afternoon counseling session
- Prior to methadone maintenance he had an 8-year history of intravenous heroin use
- Since starting methadone maintenance, he has been abstinent from heroin

John
- He is hepatitis C positive (never treated) and HIV negative
- He has been in a stable relationship with a non-drug-using girlfriend for the past 7 years
- He wants to discontinue methadone maintenance ASAP and transfer to buprenorphine so that he can “get on with my life”

John questions
- Is John a candidate for office-based opioid treatment (OBOT) with buprenorphine/naloxone? Why? Why not?
- What additional information do you need?
- If you decide John is a good candidate for transfer to OBOT with buprenorphine/naloxone what will the treatment plan include?

Susan
- 23-year-old community college student who is requesting treatment of her heroin use
- She started using oxycodone with her roommate and is now using intranasal heroin for the last 25 months, daily for the past 3 months
- She is using about 1 gram of heroin daily
- Some of her friends are now switching to intravenous use because it takes less heroin to keep from getting sick.
- She does not want to inject drugs but may be “forced” to because she cannot keep paying the “extra cost” of snorting heroin

Susan
- She has used all the money her parents gave her for school expenses to buy heroin, her credit cards are maxed out, and she has borrowed money from her friends
- Until last semester, she had an overall B average, but this semester she is in academic difficulty and has been told she will be on academic probation if her grades don’t improve
Susan

- When she doesn’t use heroin, she has anxiety, muscle aches, diarrhea and can’t sleep. She recognizes the symptoms as heroin withdrawal and was surprised because she thought she could not develop withdrawal with sniffing drugs.
- She smokes cigarettes ½ pack per day
- She drinks alcohol on the weekends up to 3 drinks per occasion
- She denies other drug use
- She has no prior history of addiction treatment

Susan questions

- Does Susan meet the criteria for DSM 5 moderate to severe opioid use disorder?
- Is Susan a candidate for office-based opioid treatment with buprenorphine/naloxone? What additional information would you need to make that decision?
- If you decide to treat Susan with buprenorphine/naloxone, what will be your treatment plan and goals?

Susan continued

- She was induced on buprenorphine in the office and given a prescription for 6 day supply of bup/nx (8/2 mg/day), and was told to participate in the clinic’s 2x per week relapse prevention group and to schedule individual counseling at an off-site program
- She was told she needed to attend the relapse prevention group in order to get her next bup/nx prescription
- She returns 3 days later having taken 6/2 mg/day for 3 days
- She has not attended the relapse prevention group nor arranged for counseling

Susan question

- What will be your treatment approach at this time?

Susan continued

- She was partially compliant with treatment for 3 weeks including attending all but 2 of the relapse prevention groups but never started counseling
- She states she has been too busy to go to counseling. She goes to school 5 days per week and has a new job working evenings as a waitress at a pub

Susan continued

- Should you require Susan to attend counseling? Why? Why not?
Susan continued

- She then returns in 4 days (3 days before her follow-up appointment) and states that one of her friends stole her buprenorphine tablets.
- Her urine is buprenorphine negative and opiate positive. She states she is sniffing heroin again to prevent withdrawal after running out of buprenorphine.
- She has been missing too many classes and has had to change her status to part-time student. She told her parents that she needs time away from school to figure out what her major should be.
- She wants “one more chance” to restart buprenorphine treatment.

Susan question

- What would you recommend for Susan at this point?

Sam

- 53-year-old maintained on buprenorphine 24/8 mg per day for the past 10 years.
- His opioid use disorder began after a motorcycle crash resulting in multiple fractures and orthopedic surgeries. He was treated with high dose morphine and quickly escalated his use and lost control of his prescriptions.
- He realized he had a problem when he ran out of his morphine and had severe withdrawal symptoms.

Sam

- He believes buprenorphine is a “miracle drug” as he believes it has saved his life. He is not in counseling but attends AA 3-4 meetings per week and has a sponsor.
- He has a history of alcoholism and has been sober for >20 years.
- He has severe chronic right knee pain which he has been told is due to arthritis after his traumatic knee injury. His pain had been well controlled on split dose buprenorphine (8x2 mg TID), ibuprofen and acetaminophen.
- Now pain is so severe, he has had to take time off from work.

Sam questions

- What do you recommend regarding his buprenorphine maintenance perioperatively?
- What do you recommend regarding his pain management perioperatively?
You are called by an ED colleague for advice on treating acute pain in your patient Mark who you are treating with buprenorphine maintenance...

- 32 y.o. male with severe, 10/10, right shoulder pain after an acute dislocation and rotator cuff tear while playing flag football
- His shoulder will be reduced and stabilized in the ED with orthopedic follow-up in 5 days

Has a 10 year history of prescription opioid use disorder
- Has been maintained on buprenorphine 16 mg SL per day for the past 2 years
- Engaged in weekly group counseling, goes to NA meetings 2-3 times per week and has had no relapses since starting office-based treatment
- He works full-time as a mechanic at a VW dealership

What would you recommend for pain management in the ED?

What would you recommend for pain management upon discharge from the ED?
Completing the Waiver Paperwork

**Item 1a: Practitioner Name**
- Name that’s on your DEA certificate.

**Item 1b: State Medical License**
- List state license where you will use buprenorphine.

**Item 1c: DEA Registration Number**
- From your DEA certificate.

**Item 2: Address of Primary Location**
- Use address that’s on your DEA certificate.

**Item 3: Telephone Number**
- Include Area Code

**Item 4: Fax Number**
- Include Area Code
Item 5: e-mail address

- Marked optional
- If filled in, you will be invited by e-mail to a discussion board website.
- Discussion board run by SAMHSA, many topics about buprenorphine, restricted to qualifying physicians.

Item 6: Notification Form

Purpose of Notification (check all that apply)

- New Notification, with the intent to immediately facilitate treatment of an individual (one) patient.*

* DOES NOT APPLY TO TODAY. Use on new form only if you are faced with an urgent need to start one patient after training is complete but before XDEA certificate is received.

Item 7: Certification of Use of Narcotic Drugs

- Check this box to certify that you will only use Schedule III, IV, or V drugs or combinations of drugs that have been approved by the FDA for use in maintenance or detoxification treatment and that have not been the subject of an adverse determination.

Item 8: Qualification Criteria

- Check box for:
  - American Society of Addiction Medicine

  - Date and location:
    - Thursday, July 29, 2015
    - Orlando, FL

Item 9: Certification of Capacity

- Check this box to certify that you have the capacity to refer patients for appropriate counseling and other appropriate ancillary services

Item 10: Certification of Maximum Patient Load

- Check this box to certify that you will not exceed 30 patients for maintenance or detoxification treatment at one time.
Item 11: Notification Form

Consent to Release Identifying SAMHSA Treatment Facility Locator

- This authorizes SAMHSA to list you on a website [http://findtreatment.samhsa.gov](http://findtreatment.samhsa.gov)
- If you want opioid-dependent patient referrals to your practice you should check

- [ ] I consent
- [ ] I do not consent