Addiction

Juliane Bohan MD, MPH
Learning Objectives

1. To discuss the neurobiology of addiction
2. To review definitions of substance abuse and dependence
3. To understand requirements for methadone dosing, drug interactions and causes of overdose.
4. To understand the various methods of benzodiazepine detoxification
Learning Objectives (Cont.)

5. To review the pathophysiology of buprenorphine, dosing instructions and safety considerations
6. To discuss issues in physician impairment and treatment options
7. To review various treatment modalities in addiction
What is drug addiction?
A chronic relapsing brain disease that is characterized by compulsive drug seeking and use, despite harmful consequences.
The Impact
## Lifetime Prevalence of Drug Use Disorders in the U.S.

<table>
<thead>
<tr>
<th>Drug Dependence</th>
<th>Men</th>
<th>Women</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lifetime prevalence:</td>
<td>9.2%</td>
<td>5.2%</td>
</tr>
<tr>
<td>12-month prevalence:</td>
<td>3.8%</td>
<td>1.9%</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Drug Abuse Without Dependence</th>
<th>Men</th>
<th>Women</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lifetime prevalence:</td>
<td>5.4%</td>
<td>3.5%</td>
</tr>
<tr>
<td>12-month prevalence:</td>
<td>1.3%</td>
<td>0.3%</td>
</tr>
<tr>
<td></td>
<td>Men</td>
<td>Women</td>
</tr>
<tr>
<td>--------------------------</td>
<td>---------</td>
<td>---------</td>
</tr>
<tr>
<td>Lifetime prevalence:</td>
<td>35.4%</td>
<td>17.9%</td>
</tr>
<tr>
<td>12-month prevalence:</td>
<td>16.1%</td>
<td>6.6%</td>
</tr>
</tbody>
</table>
Nicotine Dependence

24% Lifetime Prevalence
Substance Dependence vs. Abuse: Definitions

**Substance Dependence (ADDICTD)**
- Activities given up or reduced
- Dependence, physical: Tolerance
- Dependence, physical: Withdrawal
- Intrapersonal (internal) consequences (medical or psychiatric)

**Can’t cut down or control use**
- Time consuming
- Duration or amount greater than intended
Substance Abuse (WILD)

Clinically significant maladaptive pattern of use with one or more of the following:
- Work, school or home obligation failures
- Intrapersonal or social consequences
- Legal problems
- Danger – recurrent physically hazardous use
Risk Factors for Addiction

- Family history: 40-60% attributable to genetic factors
- Male sex
- Trauma/Abuse
- Age: Higher rates in young adults
- Ethnicity: Whites more likely to use but less likely to have physical dependence than African Americans and Hispanics
Risk Factors for Addiction (Cont.)

- Employment, social economic status and educational level (chicken and egg problem)
- Marital status: Higher in singles - those who live with a partner but never married
- Mental illness: People use drugs to self-medicate mental illness
Animals with dominant status in a group show increased numbers of dopamine receptors and are reluctant to use cocaine.

Animals with a subordinate status in a group have decreased numbers of dopamine receptors and use cocaine readily.
Estimated Economic Cost to Society Due to Substance Abuse and Addiction:

- Illegal drugs: $181 billion/year
- Alcohol: $185 billion/year
- Tobacco: $158 billion/year

Total: $524 billion/year

Addiction as a Chronic Disease

- Adaptations in the brain that result from chronic drug exposure are long lasting.
- Once chemical dependency develops, use is no longer voluntary.
- Rates of relapse and recovery in the treatment of drug addiction are equal to other medical diseases.
Why Do People Abuse Drugs?

Drugs of Abuse Engage Motivation and Pleasure Pathways of the Brain
Natural Rewards Elevate Dopamine Levels

**Food**

![Graph showing % of Basal DA Output in the NAc shell over time for food-related activities.]

**Sex**

![Graph showing DA concentration (% baseline) over sample number for sex-related activities.]

Effects of Drugs on Dopamine Release

Amphetamine

Cocaine

Nicotine

Morphine

Di Chiara and Imperato, PNAS, 1988
But Dopamine is only Part of the Story

- Scientific research has shown that other neurotransmitter systems are also affected:
  - Serotonin
    - Regulates mood, sleep, etc.
  - Glutamate
    - Regulates learning and memory, etc.
Dopamine Pathways

Frontal cortex

Serotonin Pathways

Striatum

Substantia nigra

Functions
- Reward (motivation)
- Pleasure, euphoria
- Motor function (fine-tuning)
- Compulsion
- Perseveration

Nucleus accumbens

VTA

Hippocampus

Raphe nucleus

Functions
- Mood
- Memory processing
- Sleep
- Cognition

NIDA
Medications: Mechanisms of Action

- Replacement
- Direct blockade
- Indirect blockade
- Aversion
- Reduction of craving
- Treatment of psychiatric symptoms
Replacement

Use of an agonist to reduce withdrawal and craving

Examples:
- Opiate replacement therapy – Methadone and Buprenorphine
- Using Benzodiazepines for alcohol withdrawal
Direct Blockade

Antagonists directly block the effect of the drug

Example:
- Naltrexone for opioid dependence
- Naloxone, flumazenil for acute intoxication
Indirect Blockade

Attenuation of reinforcing effects of the substance without direct blockade of the receptors bound by the drug of abuse

Example:
- Naltrexone for alcohol dependence
Aversive

Using an aversive consequence to substance use

Example:
- Disulfiram (Antabuse) for alcohol dependence
Reduction of Craving

Treating a symptom of addiction rather than the EFFECT of the drug

Example:
- Acamprosate – alcohol
- Naltrexone – alcohol and opiates
- Amantadine – cocaine
Treatment of Primary Psychiatric Disorders

- Psychiatric distress increases the risk of a substance use disorder
- Treatment of psychiatric disorders improves outcomes of substance use disorders
- Chicken and egg – which came first
- Cannot diagnose someone with a psychiatric disorder while using drugs
Pharmacotherapy as Treatment of Substance Use Disorders

- Methadone
- Buprenorphine (Subutex)
- Buprenorphine / Naloxone (Suboxone)
- Naltrexone
Opiate Addiction
Epidemiology

- 1 million heroin addicts in the U.S.
- 6.2 million prescription opiate addicts in the U.S.
- Opiates are the second most abused drug among high school seniors
- Progressive multifocal leukoencephalopathy from smoking heroin on aluminum foil
ED Visits related to heroin

1990: 33,900 ED visits

2006: 190,000 ED visits
Heroin has become more pure in the last 15 years. This has allowed other routes of administration:

- **Smoking “chasing the dragon”** – common among teenagers and young adults
- **Intranasal**
- **IV**
New Mexico

Death rate from opiate overdose:

- Number 1 in illicit drug overdose deaths
- 4 times the national rate
The chemical properties of black tar oblige IDU to:
1. thoroughly rinse syringes after each-use
2. heating is necessary to enhance drug solubility
3. black tar heroin causes vein sclerosis leading to rapid SQ & IM use
Heroin is much cheaper than prescription opiates. Often, we see patients who become addicted to pills, develop tolerance, require more and more, can no longer afford to buy them and switch to heroin.
Clinical Features of Opiate Intoxication

- Euphoria
- Apathy
- Nodding
- Miosis
- Decreased RR
- Slurred Speech
- Impaired Judgment
- Physical Evidence of Use
Clinical Features of Withdrawal

Stage I (1 – 36 hours)
- Craving, tearing, yawning, rhinorrhea, sweats

Stage II (12 – 72 hours)
- Dilated pupils, anorexia, goose flesh, tremor, irritability

Stage III (24 – 72 hours)
- Severe insomnia, N/V/D/abdominal cramps, muscle spasm, flushing, chills, violent yawning
Medical Comorbidities

- Abscesses, cellulitis, thrombophlebitis, necrotizing enterocolitis
- Endocarditis
- STDs
- Hepatitis B & C
- HIV
- Pneumonia, septic emboli, TB
- Decreased T-cells
- Seizures, brain abscesses, meningitis
Methadone

- Synthetic opioid: a full mu-opioid agonist and glutamate receptor antagonist
- Developed in Germany in 1939
- Introduced in US in 1947 by Eli Lilly and Company
- 1950: Methadone first used to treat opiate withdrawal
Methadone (Cont.)

1969: Studies by Vincent Dole showed Methadone could interrupt illicit opioid use and decrease costs to society

1972: FDA approved the use of Methadone for maintenance

Only 20% of patients with opiate addiction are on Methadone

Long $t_{1/2} = 22$ hours; analgesic activity is shorter than its half-life
Methadone (Cont.)

- Cause of 3,849 deaths in 2004 – 82% involved combinations of Methadone with benzos
- Most deaths are from tablets – not from Methadone treatment programs
A COMBINATION OF METHADONE PLUS BENZOS IS LETHAL

5x Risk of Fatal Overdose
Methadone Maintenance Programs

- Reduces or eliminates the use of illicit opiates
- Reduces criminality by 84%
- Reduces infectious diseases, especially HIV
- Hospitalization decreases by 58%
- Blocks the euphoric effects of opiates (at 80mg)
- Safer for pregnant women than heroin
Enables addicts to become more productive members of society

- Ongoing symptom management – not curative
- Counseling on-site, frequent urine drug screens
- Patients “earn” take-homes
- Provides structure to chaotic lives
Dosage

- Most patients require 80 – 120mg/day
- Retention in treatment is much higher at 80mg or more
- If patients have been without Methadone for >3 days, reduce dose by 25% and slowly work back up
- If patients have been without Methadone for >5 days, start them at 30mg and slowly work back up
Recent Heroin Use by Current Methadone Dose

J. C. Ball, November 18, 1988
DEATH RATES IN TREATED AND UNTREATED HEROIN ADDICTS


Opioid Maintenance Pharmacotherapy - A Course for Clinicians
QTc Prolongation

- If $>450$, advise decreasing the dose
- If $>500$, must decrease the dose
- Obtain history of syncope, sudden cardiac death in family – if yes, better to use Buprenorphine
- Do EKGs on patients on 100mg or more of Methadone
Pain Management in Patients on Methadone Maintenance

- NSAIDS
- Small supply of narcotics
- Patients require higher doses more frequently
- Avoid Demerol and Darvon ➔ Seizures
Methadone in Pregnancy

- Increase the dose as pregnancy progresses
- Decrease the dose after delivery
- May breastfeed as long as HIV negative
- No long-term adverse effects on infant
- Neonate typically observed for 4 days. If symptoms of withdrawal, will be placed on Methadone taper
Drug Interactions with Methadone

- Methadone is biotransformed in the liver by the Cytochrome P450–related enzymes (CYP3A4 primarily)
- Strongly bound to plasma proteins
- Stored in the liver more than the blood
CYP3A4 Inducers
(Decrease concentration)

- Rifampin
- Carbamazepine
- Phenytoin
- Phenobarbital
- St. John’s Wort
- Nelfinavir
- Efavirenz
CYP3A4 Inhibitors

(Decrease concentration)

- Fluconazole
- Fluvoxamine
- Fluoxetine
- Paroxetine
- Erythromycin
- Ketoconazole
- Cimetidine
- Ritonavir
- Amiodarone
- Ciprofloxacin
Problems with Methadone

- Sedation
- Difficult Detox
- “Diversion”
- Sweating
- Constipation
- Insomnia
- QTc Prolongation
Buprenorphine / Naloxone (Suboxone)

- Partial mu agonist
- Used for opiate replacement therapy
- Has low abuse potential
- Can be used for detox or maintenance
- FDA approved 2002
## Buprenorphine vs. Methadone

<table>
<thead>
<tr>
<th>Like Methadone</th>
<th>Unlike Methadone</th>
</tr>
</thead>
<tbody>
<tr>
<td>Reduces IVDU</td>
<td>Low potential for O.D.</td>
</tr>
<tr>
<td>Retains pt. in treatment</td>
<td>Little street value</td>
</tr>
<tr>
<td>Decreases cravings</td>
<td>No sedation</td>
</tr>
<tr>
<td>Stops withdrawal symptoms</td>
<td>Easy taper/detox</td>
</tr>
<tr>
<td></td>
<td>Can be prescribed in physician’s office</td>
</tr>
</tbody>
</table>
Why isn’t Suboxone Abused?

- When taken sublingually, Naloxone (Narcan) is not well absorbed
- When injected, Naloxone causes withdrawal
- Poor oral bioavailability – no effect if swallowed.
Onset and Duration

Onset: 30 – 60 minutes
Peak: 1 – 4 hours
Duration: 8 – 12 hours: 4mg
24 – 72 hours: 16mg
Efficacy of Buprenorphine

- Equal to Methadone
- Better than Clonidine for withdrawal symptoms
Side Effects of Buprenorphine

- HA (resolves in 3 days)
- Constipation
- Pedal Edema
- Nausea
- Dizziness
- Sweating
Overdose of Buprenorphine

- Low risk of significant problems
- No reports of respiratory depression
- May cause problems when combined with alcohol or benzos
- Less drug interactions than with Methadone
Techniques and Tips for Taking Buprenorphine

- Let dissolve under tongue
- No more than 2 tablets at a time
- Don’t smoke for 15 minutes before taking (smoking inhibits absorption)
- Don’t talk until pills are dissolved
Need to wait at least 12 hours from last heroin use to start Buprenorphine

Need to wait at least 48 hours from last Methadone use to start Buprenorphine

Methadone should be tapered down to 35mg before switching to Buprenorphine
Subutex: Pure Buprenorphine

- Primary use in pregnant women
- Used commonly in Europe for opiate withdrawal
COWS: Clinical Opiate Withdrawal Scale

- Good instrument for assessing withdrawal
- Used routinely for Buprenorphine induction
Stabilization on Suboxone

- Most patients are on 12 – 16mg/day but can go up as high as 32mg
- Ceiling effect seen at 32mg
  - Further dose increases are of no value
Buprenorphine in Pregnancy & Breastfeeding

- Subutex – not Suboxone in pregnancy
- Safe in breastfeeding
- Neonatal withdrawal from Buprenorphine is less than from Methadone
Buprenorphine and Pain Control

- If using opiates for pain, stop Buprenorphine and resume 24 hours after stopping pain meds
- Low dose Buprenorphine (2 – 4mg t.i.d) used for chronic pain
Harm Reduction Philosophy

Accepts that licit and illicit drug use is part of our society and chooses to work with drug users to prevent and minimize drug-related harm rather than ignoring or condemning it
Harm Reduction in New Mexico

Important because:

- > 80% IDU are HCV+
- Intergenerational drug use patterns
- High overdose death rates
- High DUI Rates
Harm Reduction Program Highlights

- Syringe exchange
- Overdose prevention training (Narcan)
- Hepatitis A & B vaccines
Benzodiazepines

- Lifetime use of BZDs in Methadone maintenance population is 66 – 100%
- Poor understanding by many drug users of potential harms associated with BZDs
- 80% of Methadone-related deaths in one Australian study had high levels of BZDs
- BZDs inhibit Methadone metabolism
Benzodiazepines (Cont.)

- High levels of BZDs have been identified in Buprenorphine-related deaths
- High dose BZDs can reduce respiration and potentiate Methadone’s respiratory depressant effect
Types of BZDs Abused

- Diazepam
- Alprazolam
- Temazepam
- Lorazepam

More rapid onset of action
Management of BZD Dependence

- Switch to a long-acting BZD
- Gradual taper over weeks to months
- Can use Carbamazepine
- Patient must sign ROI so that all prescribing physicians can be notified of benzo taper
- Regular UDS monitoring
Naltrexone

- Opioid receptor antagonist
- Better for alcohol dependence than opiate dependence
- Longer acting than Naloxone
- Depot injectable form: Vivitrol lasts 30 days
- LFTs should be less than twice normal
Naltrexone (Cont.)

- Must be Opioid free for 7 – 10 days
- If patient on Naltrexone requires opioid analgesia, the amount of opioid required may be greater than usual; watch for respiratory depression.
Other Treatment Modalities for Addiction

- 12-Step Programs
- Motivational Interviewing
- Drug Court
12-Step Programs

- Consistent involvement is associated with better outcomes
- 67% probability of remaining sober and involved in AA for those with 1-year of sobriety
- 85% for those with 2 – 5 years of sobriety
- 90% for those with >5 years of sobriety
Motivational Interviewing

- **O**pen-ended questions
- **A**ffirm the person
- **R**eflect what the person says
- **S**ummarize the person’s own perspective of change

A collaborative approach in which the counselor evokes the patient’s own motivation and resources for change.
Motivational Interviewing (Cont.)

“What are the good things about your drug use?”

“What are the not-so-good things about your drug use?”
Motivational Interviewing (Cont.)

- Often providers try to convince people of the reasons they should change – this is not effective.
- Instead, have the patient come up with what he wants to do.
- Make sure the patient has buy-in.
Drug Court

- Combining criminal justice sanctions with drug treatment is effective in decreasing drug use and crime
- Individuals under legal coercion stay in treatment longer and do as well or better than those not under legal pressure
Prison-Based Treatment Programs

- Relapse to drug use and recidivism to crime are significantly lower if the drug offender continues treatment after returning to the community.

- Many prisons and jails are starting Suboxone at time of release.
Principles of Effective Treatment for Drug Addiction

- No single treatment is appropriate for all individuals
- Treatment must be readily available
- Effective treatment attends to multiple needs of the individual (medical, social, psychological, vocational)
- Remaining in treatment for an adequate period is critical (3 months is when significant improvement is reached)
Principles of Effective Treatment for Drug Addiction (Cont.)

- Counseling is a critical component of treatment
- Medications are an important element of treatment
- Co-occurring mental disorders must be simultaneously treated
- Medical detox does little to change long-term drug use
Principles of Effective Treatment for Drug Addiction (Cont.)

- Treatment does not need to be voluntary to be effective
- Continuous monitoring of possible drug use is essential
- Relapses are part of the disease of addiction
- Recovery requires multiple episodes of treatment
Cocaine, Methamphetamine

- No medication is effective treatment
- Amantadine used to decrease cocaine craving but with mixed results
- Vaccine for cocaine dependence is under investigation
- Levamisole-contaminated cocaine leads to agranulocytosis
The Addicted Physician

- Physicians are less likely to smoke cigarettes and more likely to consume BZDs and opiates (unsupervised) than the general population.
- Physicians are 5 times more likely to take sedatives and minor tranquilizers without medical supervision than the general population.
Age of Presentation: Bimodal Distribution

- First presentation for treatment: Physician in training and early practice
- Second presentation: Mid-late career
Specialty

- Highest substance use in Psychiatrists, Anesthesiologists and Emergency Medicine Physicians
- Family Medicine overrepresented in many addiction programs
- Lowest substance use in Pediatricians and Surgeons
Anesthesiologists more likely to use highly potent opioids

ENTs and Plastic Surgeons more likely to use cocaine

Psychiatrists more likely to use BZDs
Specialty (Cont.)

- Emergency Medicine Physicians
  - Twice as likely to use marijuana
  - Cocaine use is high
  - More likely to smoke tobacco (along with Surgeons)
Drugs Abused by Physicians

# 1 – Alcohol

# 2 – Opioids
Anesthesiologists

- Display an accelerated course of addiction (tolerance) when using the most potent opioids ➔ rapid downhill course

- This is why Anesthesiologists are over-represented in physician treatment programs
Physician Health Programs (PHPs)

- In 2007, 9000 Physicians were in monitoring programs across the U.S.

- Most states have “snitch” laws requiring hospital and colleagues to report to state PHP.
Controversies Inherent in Physician Addiction

- Should employed physicians be treated with Methadone or Suboxone?
- Should physicians on opioids for chronic pain be allowed to practice?
- Are opioid-addicted Anesthesiologists safe to return to their profession after treatment?
Malpractice insurer often won’t cover physicians on opiate replacement therapy
“First the man takes a drug, then the drug takes a drug, then the drug takes the man”

Chinese proverb