DRUGS OF ADDICTION:

A Survey of their Pharmacology & Pathophysiology

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BACKGROUND:
Douglas L. Bovee, MD

- Pharmacy and pharmacology background
- Medical school
- Residency in Internal Medicine
- Adult primary care
- Addiction Medicine: diagnosis, treatment and referral of drug dependent patients, tx of complications, and education
- Active in the realm of health care systems and public health
Goals

- Inform group about personally and professionally important material
- Reinforce some of the material presented in other parts of the course
- Personalize the value of the info
- Connect the material to current news
- Stimulate further inquiry and/or research into addiction medicine
Addiction is a primary, chronic disease of brain reward, motivation, memory and related circuitry. Dysfunction in these circuits leads to characteristic biological, psychological, social and spiritual manifestations. This is reflected in an individual pathologically pursuing reward and/or relief by substance use and other behaviors.
Definition of Alcoholism

A disease characterized by continuous or periodic:

- Impaired control over drinking
- Preoccupation with the drug ethanol (beverage alcohol)
- Use of alcohol despite adverse consequences
- Distortions of thinking, most notably denial
Characteristics of Addiction

- Loss of control
- Craving and compulsion
- Continued use despite adverse consequences
Reward center
Reward Pathway

This system is activated by drugs of abuse

Ventral tegmental area

Median forebrain bundle

Dopamine

Nucleus accumbens
Pharmacokinetics: the study of the movement of a drug thru the body

- Absorption
- Distribution (Where does the drug go?, storage?)
- Metabolism (Where and how is it broken down? Are the metabolites also active or toxic?)
- Excretion (How is the drug and its metabolites removed from the body?)
- Half life and duration of action
ETHANOL

- **Chemistry:** CH$_3$-CH$_2$OH
- **Absorption:** mostly intestines; also stomach and lungs
- **Metabolism:**
  
  \[
  \text{CH}_3\text{CH}_2\text{OH} + \text{NAD}^+ \rightarrow \text{CH}_3\text{CHO} + \text{NADH} + \text{H}^+ \\
  \text{CH}_3\text{CHO} + \text{H}_2\text{O} + \text{CoA} + \text{NAD}^+ \rightarrow \text{CH}_3\text{COO}^-\text{CoA} + \text{NADH} + \text{H}^+
  \]
<table>
<thead>
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<th>Systemic Effects of Alcoholism</th>
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<td>Signs of trauma</td>
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<td>Infestation</td>
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<td>Fracture</td>
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<td>Subdural hematoma</td>
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<td>Other trauma</td>
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<td><strong>Mouth</strong></td>
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<td>Nutritional stomatitis</td>
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<td>Cheilosis</td>
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<td>Increased incidence of cancers</td>
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<td><strong>Eyes</strong></td>
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<td>&quot;Tobacco-alcohol&quot; amblyopia</td>
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<td>Ophthalmoplegia (Wernicke-Korsakoff syndrome)</td>
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<tr>
<td><strong>Gastrointestinal</strong></td>
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<td>Esophagus</td>
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<td>Esophagitis</td>
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<td>Diffuse esophageal spasm</td>
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<td>Mallory-Weiss tear</td>
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<td>Rupture with mediastinitis</td>
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<td>Increased incidence of cancers</td>
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<td><strong>Stomach and duodenum</strong></td>
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<td>Acute erosive gastritis</td>
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<td>Chronic hypertropic gastritis</td>
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<td>Peptic ulcer</td>
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<td>Hematemesis</td>
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<td>Increased incidence of cancers</td>
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<td><strong>Bowel</strong></td>
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<td>Malabsorption</td>
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<td>&quot;Alcoholic diarrhea&quot;</td>
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<td><strong>Liver</strong></td>
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<td>Steatosis</td>
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<td>Alcoholic hepatitis</td>
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<td>Cirrhosis</td>
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<td><strong>Pancreas</strong></td>
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<td>Acute pancreatitis</td>
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<td>Chronic recurrent pancreatitis</td>
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<td>Calcific pancreatitis</td>
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<td>Exocrine pancreatic insufficiency</td>
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<td>Pseudocyst</td>
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<td><strong>Respiratory</strong></td>
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<td>Increased susceptibility to infection</td>
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<td>Fractured ribs</td>
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<td><strong>Cardiovascular</strong></td>
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<td><strong>Cardiomyopathy</strong></td>
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<td><strong>Beriberi</strong></td>
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<td><strong>Genito-urinary tract</strong></td>
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<td>Hypogonadism (in men)</td>
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<td>Impotence (in men)</td>
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<td>Infertility (in women)</td>
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<td><strong>Endocrine and metabolic</strong></td>
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<tr>
<td>Decreased testosterone</td>
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<td>Hyperglycemia</td>
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<td>Hypoglycemia</td>
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<td>Hyperlactatemia</td>
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<td>Hyperuricemia</td>
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<tr>
<td>Metabolic acidosis</td>
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<td>Respiratory acidosis</td>
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<td>Alcoholic ketoacidosis</td>
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<td>Hypophosphatemia</td>
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<td>Hypermetabolism</td>
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<td>Hypokalemia</td>
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<td>Hypomagnesemia</td>
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<td>Hypercholesterolemia</td>
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<td>Hypertriglyceridemia</td>
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<td>Protein malnutrition</td>
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<td>Hypotransferrinemia</td>
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<tr>
<td>Vitamin B deficiencies</td>
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<td><strong>Neurologic</strong></td>
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<td>Acute intoxication withdrawal syndromes</td>
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<td>Amblyopia (optic neuropathy)</td>
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<td>Wernicke-Korsakoff syndrome</td>
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<td>Cerebellar degeneration</td>
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<td>Polyneuropathy</td>
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<td>Pellagra</td>
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<tr>
<td>Marchiafava-Bignami disease</td>
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<tr>
<td>Central pontine myelinolysis</td>
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<tr>
<td>Cerebral atrophy, dementia</td>
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<tr>
<td>Myopathy</td>
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</table>
UGI Tract, liver, and pancreas
Brain
Fetal-Alcohol Syndrome

- Leading cause of mental retardation in western countries
- No known safe level of drinking during pregnancy
- Led to warning levels on alcoholic beverages
Mechanism of action: Ethanol on the brain

- Triggers release of endorphins
- Membrane effect
- Interacts with GABA and glutamate receptors
Alcohol $\rightarrow$ Endorphins $\rightarrow$ Euphoria

\[ \text{Naltrexone} \times \]

$\mu$ receptors $\rightarrow$ Euphoria
Pharmacodynamics: The study of drug action in the body (especially drug-receptor interaction)

- **Antagonist**: a drug that blocks a receptor
- **Agonist**: a drug that mimics the action of an endogenous chemical
- **Partial agonist**: a drug that acts as an agonist but has a ceiling on its ability to stimulate a receptor.
Drug-Receptor Coupling

- Neurotransmitter

- Agonist

- Antagonist

Receptor Site Interactions

gives pharmacological response

gives NO pharmacological response
Conceptual Representation of Opioid Effect Versus Log Dose for Opioid Full Agonists, Partial Agonists, and Antagonists*
Endorphins: endogenous + morphine

generic term referring to the 3 families of endogenous opioid peptides:

Enkephalins, Dynorphins & Endorphins
Endogenous opioids

Work to decrease the release of excitatory neurotransmitters (thus are natural tranquilizers)

- Endorphins
- Enkephalins
- Dynorphins

All work on different types of opioid receptors

- Mu (OP3)
- Delta (OP1)
- Kappa (OP2)
Opioids

- Very effective for analgesia.
- Major toxicity due to impurities; needle use with associated illnesses like HCV, HIV, and skin infections; and illegal behavior necessary to gain resources to purchase drug.
- Overdose leads to respiratory depression.
- In pure form very addictive but not especially toxic.
Rates of prescription painkiller sales, deaths and substance abuse treatment admissions (1999-2010)

Percent of overdose deaths by type of drug, Oregon, 2012*

*Primary cause of death on death certificates

<table>
<thead>
<tr>
<th>Drug</th>
<th>Percent deaths</th>
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<tbody>
<tr>
<td>Prescription opioids</td>
<td>32%</td>
</tr>
<tr>
<td>Heroin</td>
<td>16%</td>
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<tr>
<td>Alcohol</td>
<td>16%</td>
</tr>
<tr>
<td>Sedative hypnotic, antiepileptic, psychotropic</td>
<td>14%</td>
</tr>
<tr>
<td>Other unspecified</td>
<td>10%</td>
</tr>
<tr>
<td>Psychostimulants</td>
<td>7%</td>
</tr>
<tr>
<td>Benzodiazapines</td>
<td>3%</td>
</tr>
<tr>
<td>Unspecified narcotics</td>
<td>2%</td>
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</tbody>
</table>
Opioid Overdose

- 2014 -- 47,000 drug overdose deaths. 61% (28,670) involved an opioid (often fentanyl or derivative). This is more than 7 times the 4,000 people killed by these drugs in 1999.

- 78 people die each day in USA from an opioid related overdose

- Naloxone can immediately reverse an overdose and can be delivered in the community.
Signs of Opioid Overdose

- Extreme sleepiness, inability to awaken verbally or upon sternal rub.
- Breathing problems that can range from slow to shallow breathing in a patient who cannot be awakened.
- Fingernails or lips turning blue/purple.
- Extremely small “pinpoint” pupils.
- Slow heartbeat and/or low blood pressure.
Abuse and Use of Opioids

- Heroin: to get high
- Morphine and others: for pain relief
- Methadone and buprenorphine: to treat opioid dependency
- Naloxone: to treat opioid overdose
- Naltrexone: to treat alcoholism and opioid dependency
Affinity and Dissociation

- **Affinity:**
  Strength with which a drug binds to its receptor
  (Strength of binding is not related to activation or efficacy at the receptor)

- **Dissociation:**
  Speed (slow or fast) of disengagement or uncoupling of drug from the receptor
Affinity and Dissociation

**Buprenorphine** has:

- high affinity for mu opioid receptor—competes with other opioids and blocks their effects
- slow dissociation from mu opioid receptor
- prolonged therapeutic effect for opioid dependence treatment
Buprenorphine Summary

- Buprenorphine a partial mu agonist opioid with high affinity and slow dissociation thus also acts as exogenous opioid blocker

- Profile of effects similar to other mu agonist opioids, but less risk of respiratory depression, lower level of physical dependence

- Can be abused, but combination with naloxone decreases abuse potential
LM, 42yo woman

- 12/08 presented on referral from methadone program for consideration of switch to buprenorphine.

- Hx of IV heroin use 1g/d. Started methadone program 7/06 and last heroin, 8/06.

- Over next 2 yrs stabilized and got 13 TOs.

- 1/09, switched to buprenorphine thru induction process.
LM continued

- Initially stabilized on 8mg but dose increase slightly 9/12 and 4/13 due to cravings.
- Has been stabilized on 8mg bid since then.
- Her professional life has grown since on buprenorphine to working full time at hospital.
- Her personal life has stabilized as well.
- She goes to 3 12 step meetings weekly and has quit smoking.
Neurosynapse and Neurotransmitters

The structures and chemicals that allow one nerve cell to communicate with another
COCAINE’S LOCAL ANESTHETIC AND SYMPATHOMIMETIC EFFECTS

D = COCAINE BLOCKS SODIUM CHANNELS OF NON-MYELINATED FIBERS THUS SLOWS OR BLOCKS ACTION POTENTIALS.

A = STIMULATE RELEASE
B = BLOCKS REUPTAKE (E, NE, DA, 5HT)
C = STIMULATE SYNTHESIS (E, NE, DA)
    BLOCKS SYNTHESIS (5HT)
Cocaine and Amphetamines: Stimulants of the central nervous system

- Increase blood pressure
- May increase or decrease pulse
- Increase body temperature
- Dilate pupils
Stimulants: cocaine, amphetamines, and others

- Cocaine: formally used as local anesthetic
- Amphetamines and others: effective for attention deficit disorder (e.g. methylphenidate) and sometimes used for weight loss
- Potentially very toxic to CNS and heart
- May cause psychosis
- Intranasal use causes nose damage
Pharmacokinetics of Drugs of Addiction

Drug delivery: process and systems

- Oral (usual stomach transit time about 1 hr.)
- Parenteral: IV, IM, and subcutaneous
- Inhalation (e.g. smoking or with vaporizer)
- Transmucosal (i.e. snorting, sublingual)
- Transdermal (e.g. patches and gels)
Circulation
The real reason dinosaurs became extinct
Nicotine

- Not especially toxic but very addictive.
- Usually delivered by smoking tobacco.
- Tobacco smoke with over 4000 chemicals—at least 50 are known carcinogens.
- Tobacco smoking is leading preventable cause of death in USA.
Absorption & Fate of Cigarette Smoke

Tobacco smoke is comprised of:

1. Cigarette constituents:
   - Organic matter
   - Nicotinic alkyloids
   - Additives

2. Pyrolysis products:
   - CO₂
   - CO
   - TAR

Smoke production by pyrolysis (1600–1800°F)

Filter traps some particulates

Main stream smoke

Side stream smoke

M.S. smoke

To lungs where absorption occurs

Absorption factors:
- Inhalation amount
- Inhalation depth
- Inhalation duration
- pH of smoke
- Absorption characteristics of individual constituents
Electronic Cigarettes (e-cigs)

- **Device**: mouthpiece and 2 interlocking plastic tubes. **Distal tube is rechargeable battery.** Proximal tube is a cartridge with heating element and liquid nicotine and propylene glycol or glycerol reservoir.

- Some cartridges have impurities including polycyclic aromatic hydrocarbons.

- Lipoid pneumonia from use has been reported.
Marijuana/THC

- Works on CB1 (most common receptor in the brain) and CB2 receptors (mostly on immune cells).
- Impairs learning, judgment, and reaction time (Recent studies show early onset marijuana smokers demonstrate significantly worse performance on cognitive tasks and the effect is dose related).
- Effective for appetite stimulation, spasticity, nausea, seizures, and pain. Maybe useful for cancer.
- Cannabinoids vaporize at about 200 deg F
Endocannabinoids

- Anandamide and 2-archadonylglyceride (2AG)
- Cells release chemicals locally and interact with local cells (paracrine system)
- Action on CB-1 receptors leads to net anabolic action (i.e. net increase in energy intake and storage).
- Includes: Stimulates food intake, increases storage of fat, stimulates the liver to increase de-novo synthesis of fatty acids, and reduces sensation of satiety.
Cannabidiol and THC
Cannabidiol (CBD)

- Major component of Marijuana
- Partial antagonist at CB1 receptors
- Blocks breakdown of anandamide
- Does not lead to euphoria
- Appears to be useful for spasticity, seizures, and pain and perhaps cancer.
- Approved in many countries and under study in USA
QUESTIONS
**Endocannabinoid Receptors**

**CB-1**
- Brain Structures
- Controlling Energy Intake
  (eg, Hypothalamic Hunger-Satiety Center)

**CB-2**
- Leukocytes/WBCs
- Immune & Inflammatory Reactions
  (eg, Lymphocytes & Macrophages)

**Metabolic & Eating Disorders**
1. Abdominal Obesity
2. Dyslipidemia
3. Hyperglycemia

http://www.jimmunol.org/content/165/1/373.full?ijkey=YriEsKcvAs2z.
Prescription Drug Abuse

- 2010: about 12 million Americans (age 12 or older) reported nonmedical use of prescription painkillers in the past year.
- 1997-2007: 74mg/person opioid to 369mg/person, increase of 400%.
- 2000-09: 1,200 Overdose deaths in OR due to prescription pain killers.
- Drug overdose death rate increased from 12.3 per 100K in 2010 to 16.3 per 100K in 2015.
Triple Aim of Health Care Transformation

- Improve patient care—esp the individual’s experience of care
- Improve health outcomes—ie improve health of our community
- Reduce costs—Currently health care costs are the biggest driver of our increasing national debt
Ally, now 27yo woman

- U/O student, single, smoker
- Problems with alcohol age 16 including crashed car
- Age 17 started using OxyContin
- Switched to heroin snorting then IV
- Consult 8/08, age 20
Ally, Continued

- 2008, Started on buprenorphine 4mg
- No other opioids since on buprenorphine
- 7/09, Started taper with decrease to 3mg
- Summer, 2009, quit smoking
- 10/09, decreased to 2mg
- 11/09, decreased to 1mg
- 1/10 stopped—had mild withdrawal
Casey

- Late 30s yo man, married, works full time for sporting goods company
- Hx of smoking heroin many yrs ago
- Hx of kidney stones and anxiety disorder
- Was using Percoset, morphine, Dilaudid, or OxyContin up to 40 tablets/day
- 10/03, Detoxed at Buckley House
- 10/03, Serenity Lane residential TX
Casey, 2004

- Relapsed to high dose oral opioids
- 6/04, admitted to opioid agonist treatment program (IHC) using methadone
- Dose up to 80mg to help with anxiety as well as addiction
- Tapered down to 35mg over 3mo.
- 2/15/05, Suboxone induction done
Casey on buprenorphine

- 2/17/05, c/o diarrhea, cold, chills, rhinorrhea, antsy
- Dose increased up to 32mg over the next month
- 4/12/05, Feels “normal” and “got stabilized”
  Says “grateful” for med
- Now on 16mg/d after slow taper. Feeling well
  and doing well with family and work.
Prescription painkillers sold by state per 10,000 people (2010)

SOURCE: Automation of Reports and Consolidated Orders System (ARCOS) of the Drug Enforcement Administration (DEA), 2010
“I was smoking 40 a day, but now I’m down to just two.”
JH, 33yo man

- Consult last year at local hospital.
- Grew up in drug using and dealing home and started MJ and EtOH as teen.
- Married, separated, homeless for 2 yrs.
- 9th grade education, GED, and worked on poultry farm for 10 yrs but lost job due to amphetamine use.
- Later turned to heroin and recently ½ g/d IV
- Admitted New Years Eve to hospital due to severe fatigue.
Found to have MRSA bacteremia.

Recovered with antibiotic treatment.

Wanted help with his addiction.

Started on Suboxone and quickly stabilized.

1 yr later much improved on Suboxone with greatly reduced drug use and no hospitalizations.

Still homeless but looking for work.

Says going to 12 step meetings.