Opioid Use Disorder

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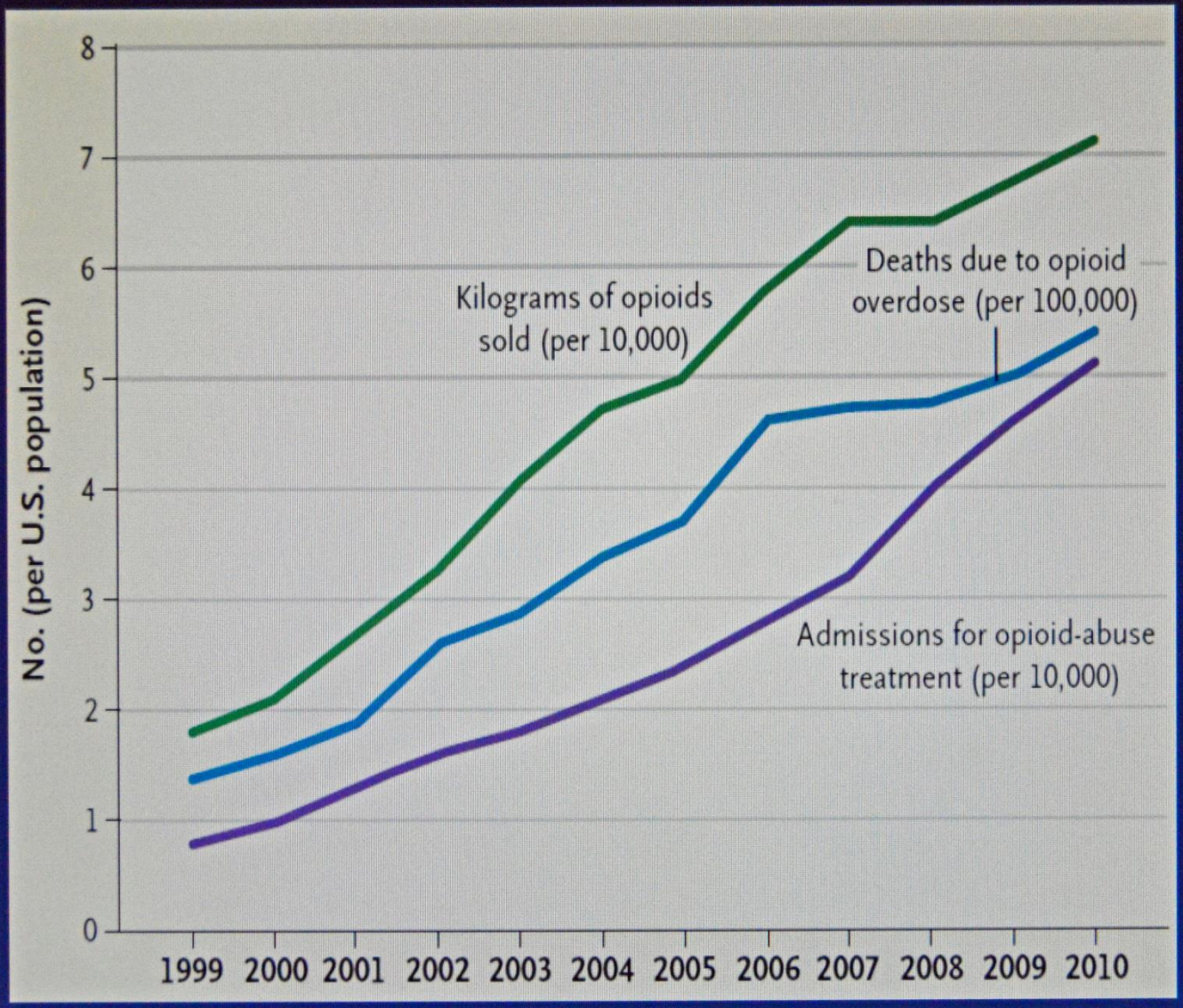
Objectives

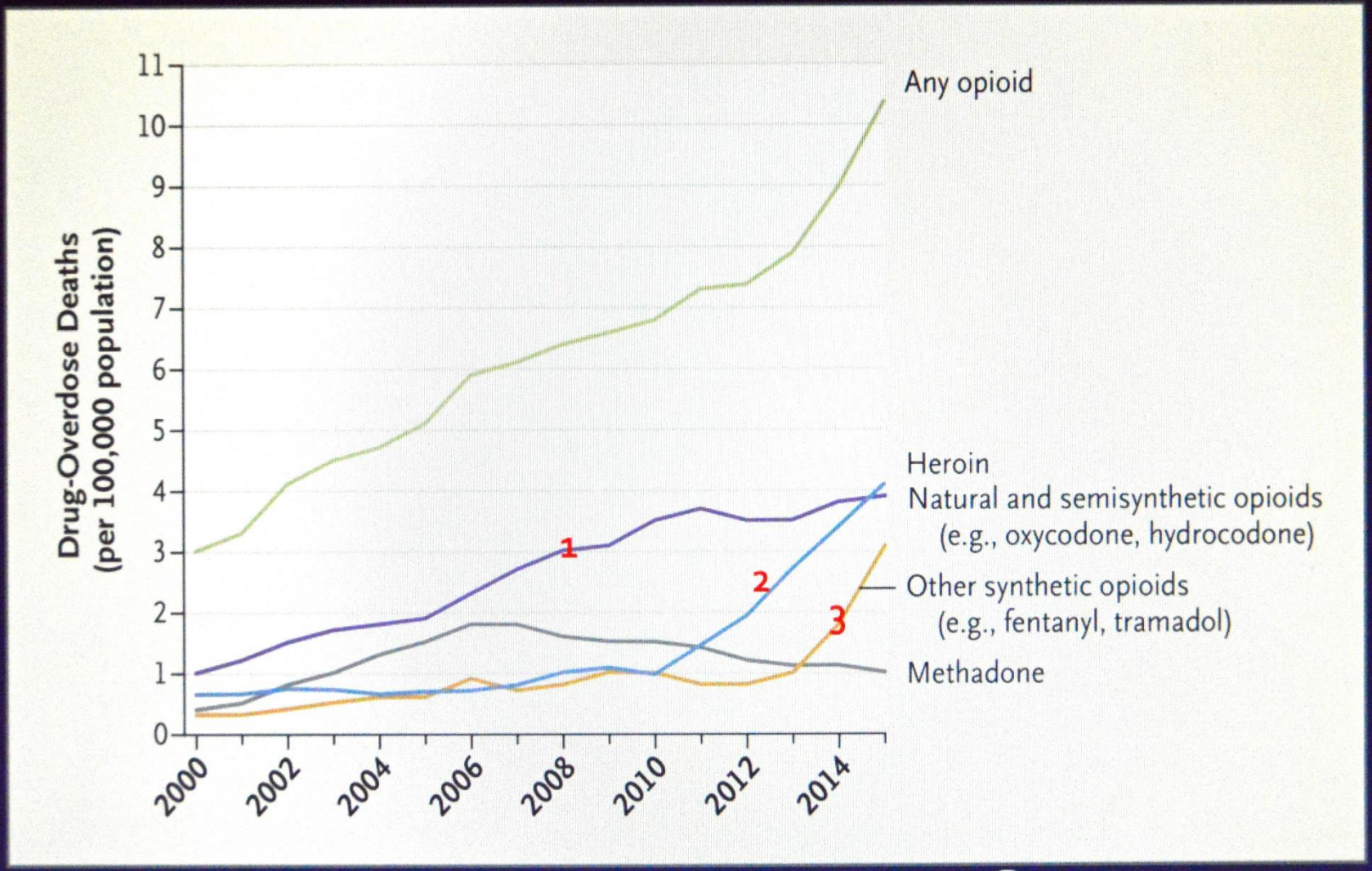
- Increase understanding about opioid use disorder (OUD)
- Identify risk factors for cross-addiction, relapse, and overdose
- Increase insight about overdose reversal and tools to prevent death

Prescription Opioid Trends: 1999-2010



National Vital Statistics System, 1999-2008; Automation of Reports and Consolidated Orders

Drug-Overdose Deaths Involving Opioids, by Type of Opioid, United States, 2000–2014



Frank RG, Pollack HA. N Engl J Med 2017;376:605-607.

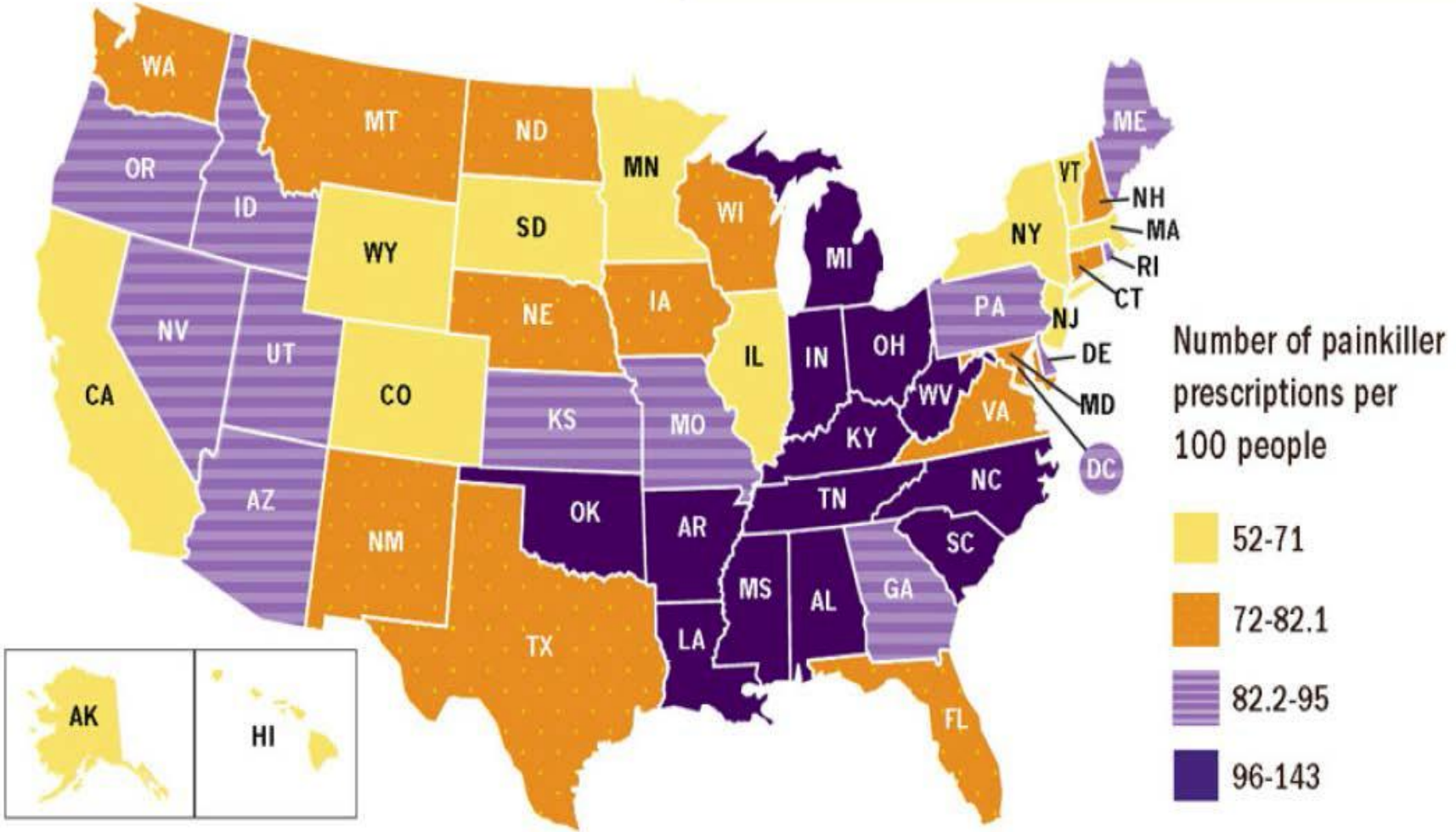
The NEW ENGLAND JOURNAL of MEDICINE

Fentanyl Chest Wall Rigidity

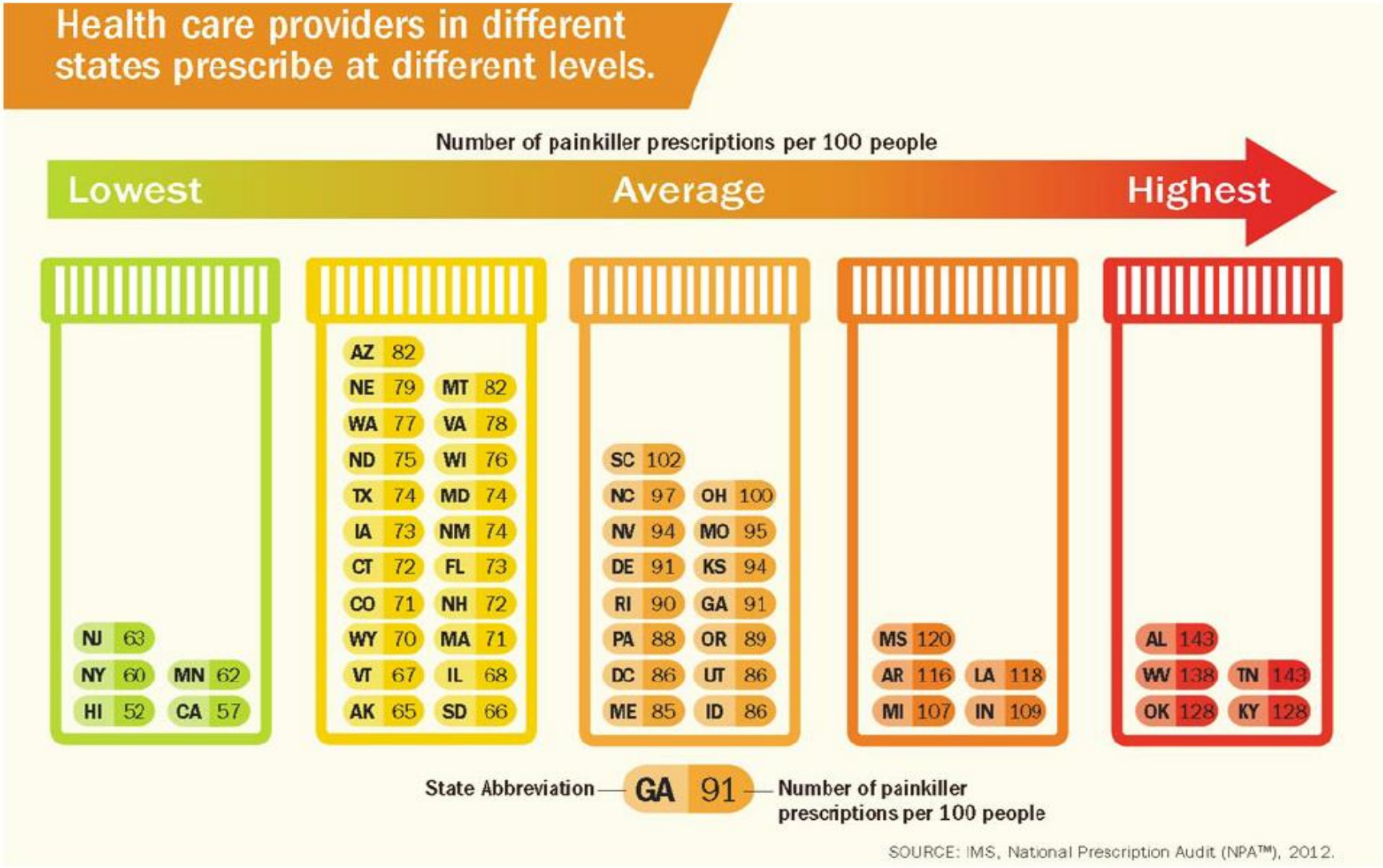
- First Reported in 1953 in anesthesia literature
- Skeletal Muscle Rigidity: Chest Wall Most Common
- Most common with fentanyl and its congeners (lipid solubility)
- Most common with rapid IV administration
- Activation of the coerulospinal noradrenergic pathway, following mu receptor activation in LC
- Not dose related
- Reversed with naloxone (IV route in literature)
- Ventilatory Support
- Low or Absent Norfentanyl (appears in 2 minutes: CYP3A4(Inhb)

Burns, G et al Clinical Toxicology, Vol 54, No 5, 420-23, 2016

Some states have more painkiller prescriptions per person than others.



SOURCE: IMS, National Prescription Audit (NPA™), 2012.



Health care providers in different states prescribe at different levels.

This graphic orders the fifty states plus the District of Columbia by the number of painkiller prescriptions per 100 people. There are five pill bottles:

- The green bottle contains states that have the lowest number of prescription painkillers per 100 people: 52-63 (5 states).
- The yellow bottle contains states that have 65-82 prescription painkillers per 100 people (21 states).
- The orange bottle contains states that have 85-102 prescription painkillers per 100 people (15 states).
- The red-orange bottle contains states that have 107 to 120 prescription painkillers per 100 people (5 states).
- The red bottle contains states that have the highest number of prescription painkillers per 100 people: 128-143 (5 states).

What are Opioids?

- A class of drugs found within opium as well as semi-synthetic and synthetic compounds that resemble the structure and/or function of the naturally occurring forms.

Type	Source	Examples
Natural Opiates	Poppy	Morphine, Thebaine, Codeine, Opium
Semi-Synthetic	Poppy—but more processed	Heroin, Oxycodone
Synthetic	Designed in Lab	Methadone, Fentanyl

What Do Opioids Do?

- Stimulate opioid receptors in central nervous system and gastrointestinal tract
- Analgesia – pain relief (somatic & psychological)
- Antitussive action – cough suppression
- Antidiarrheal
- Respiratory depression
- Euphoria

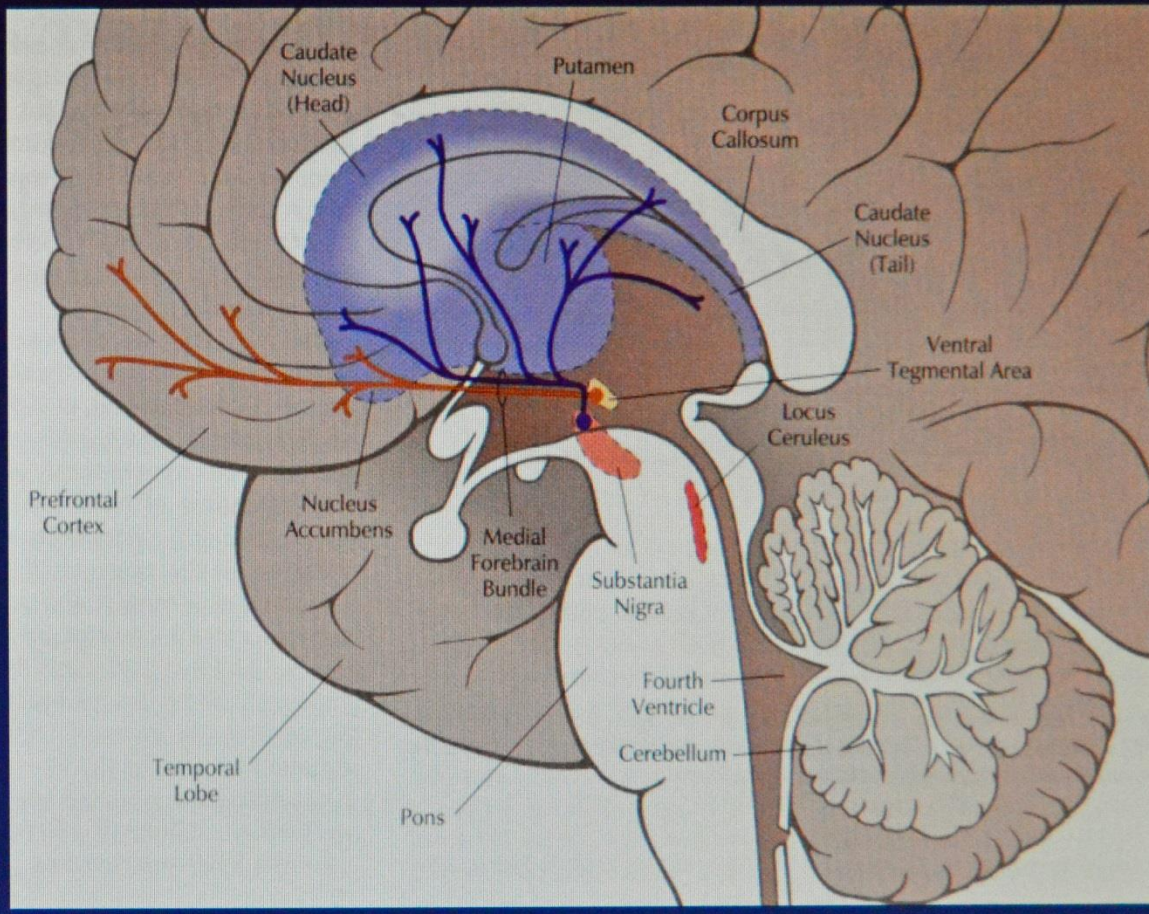
Effects on the Body

- Nausea, vomiting
- Drowsiness, sedation
- Skin changes—rash, bumps; flushing, cooling of skin; cold, clammy
- Constricted pupils (miosis)
- Constipation
- Respiratory depression
- Changes in heart rate, blood pressure
- Muscle rigidity (myoclonus)
- Psychological effects—euphoria, hallucinations, delirium, dizziness, confusion, headache, memory loss

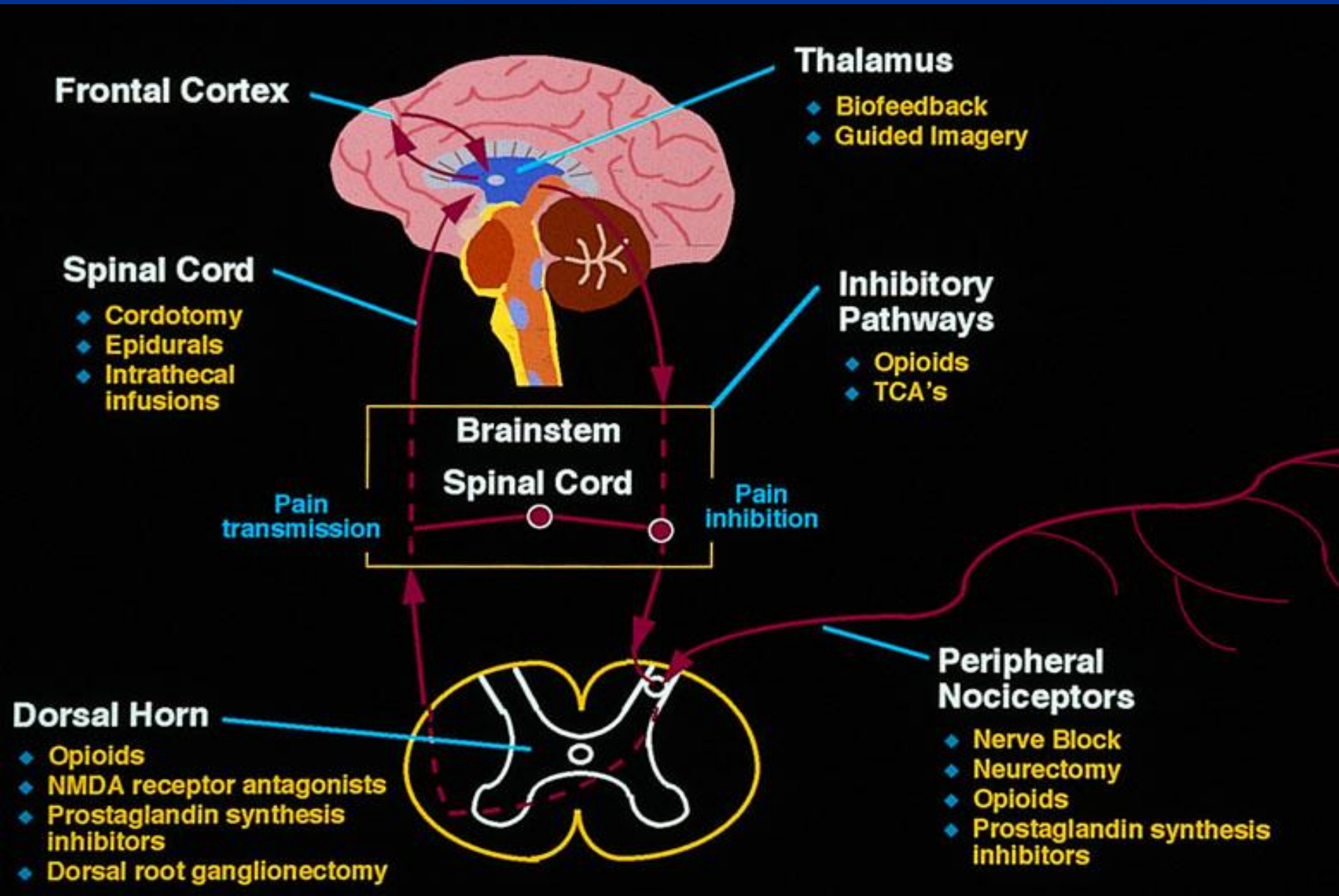
Reward/Reinforcement

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



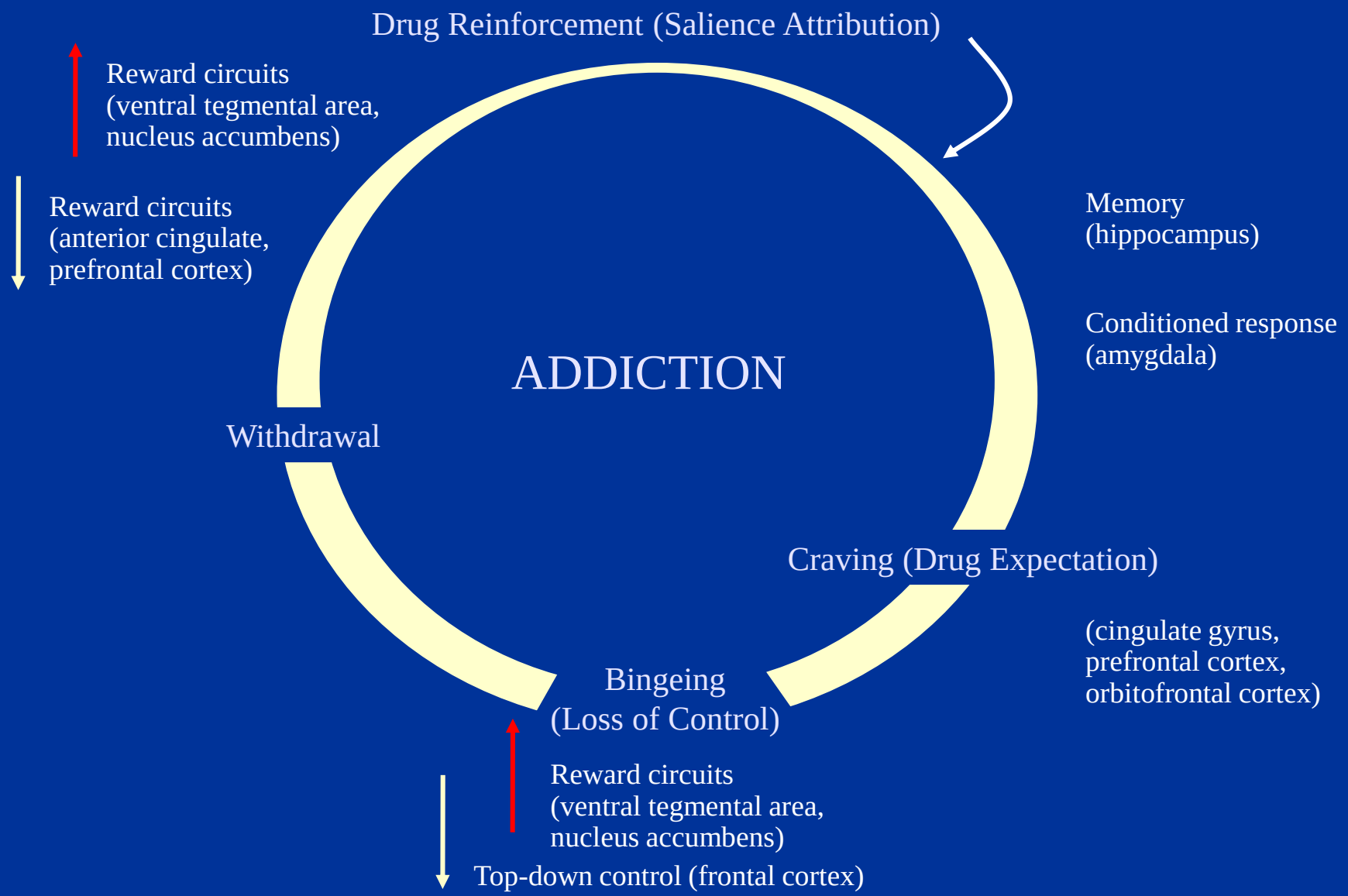
Targets for Pain Treatment



Additional Medical Complications

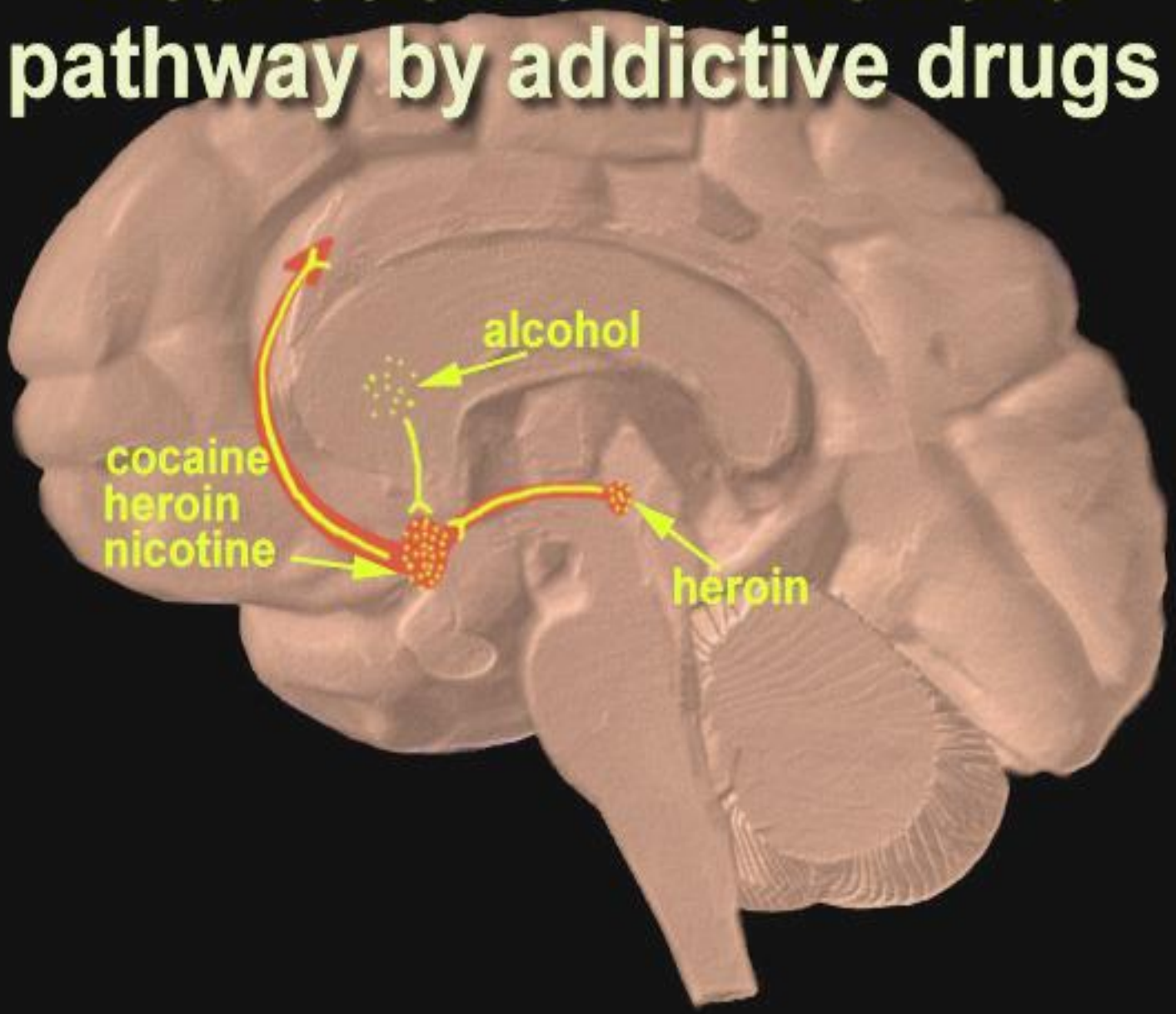
- Overdose:
  - Decrease central nervous system functioning results in medical distress, including death
  - Opioids, primarily prescription pain relievers and heroin are the main drugs associated with overdose deaths.
- Unsterile needle use and sharing:
  - HIV
  - Hepatitis B, C
- Lifestyle:
  - STD
  - TB

Integrative Model of Brain and Behavior: the I-RISA (Impaired Response Inhibition and Salience Attribution) Syndrome of Drug Addiction



Goldstein and Volkow, Am J Psychiatry, Oct. 2002.

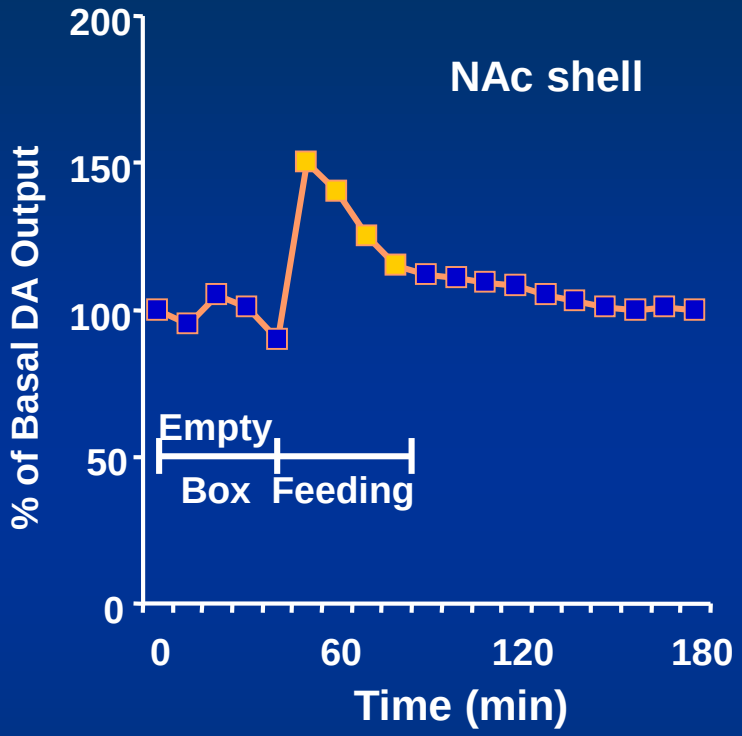
Activation of the reward pathway by addictive drugs



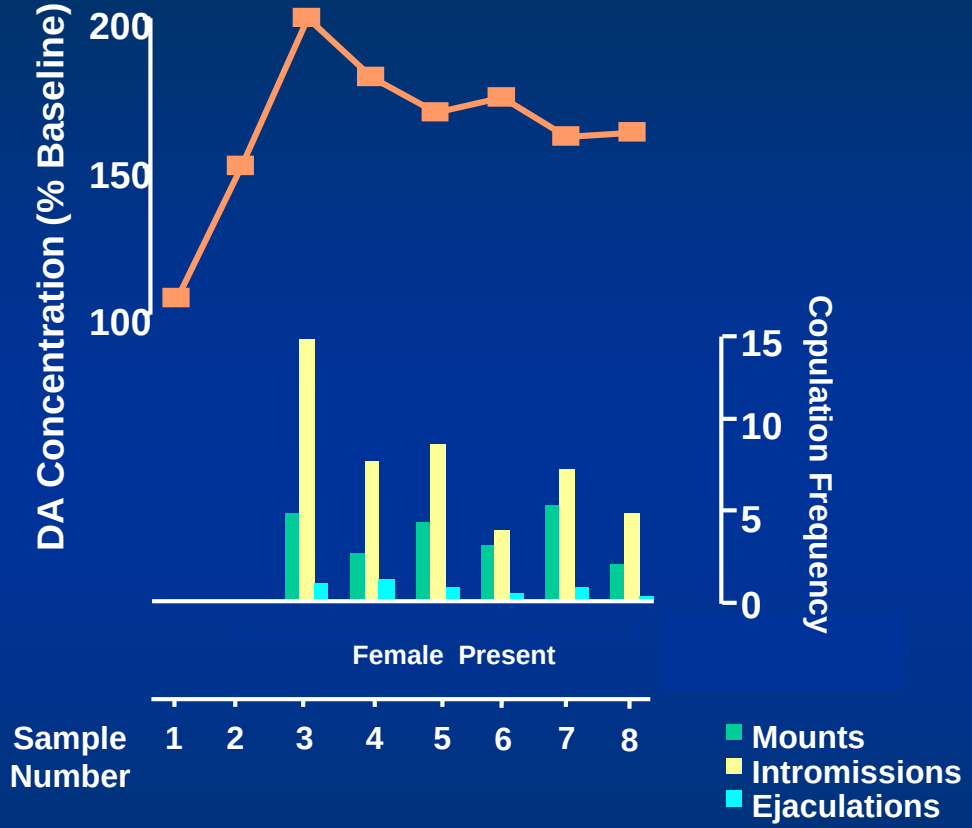
Natural Rewards

- Food
- Fluid
- Sex
- Excitement
- Comfort/Friendship

Natural Rewards Elevate Dopamine Levels

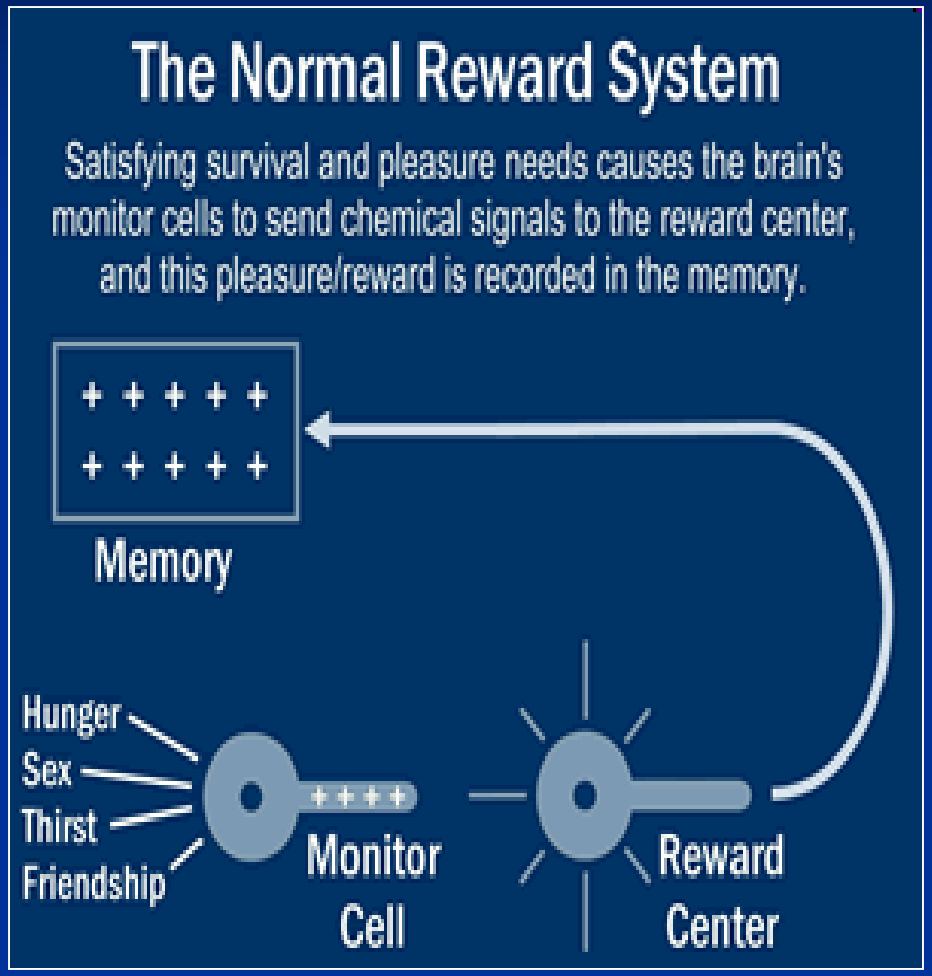


Di Chiara et al., Neuroscience, 1999.

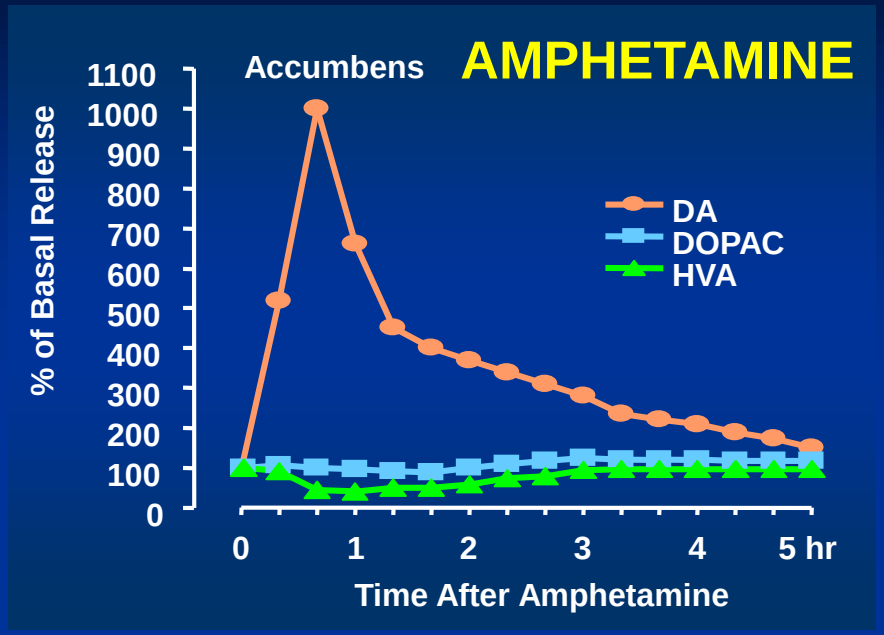


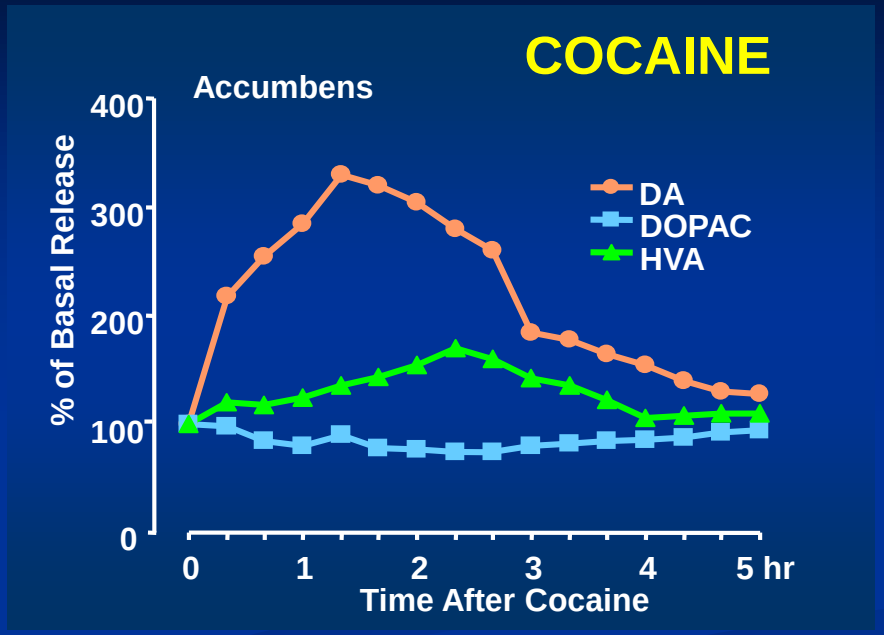
Fiorino and Phillips, J. Neuroscience, 1997.

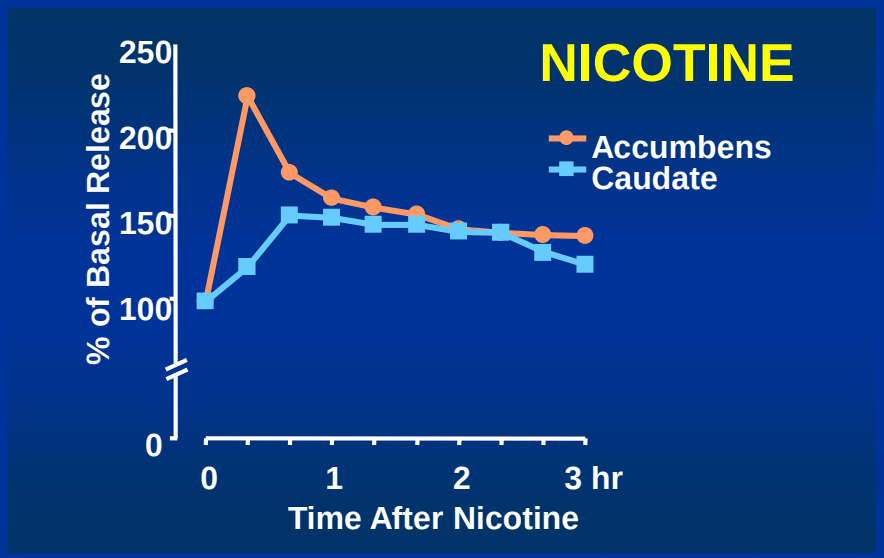
Reward Brain System

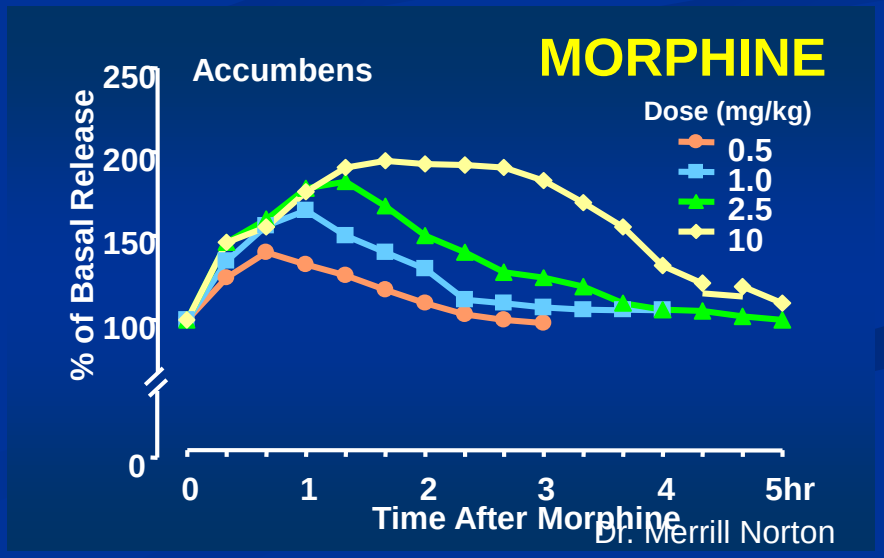


Effects of Drugs on Dopamine Release





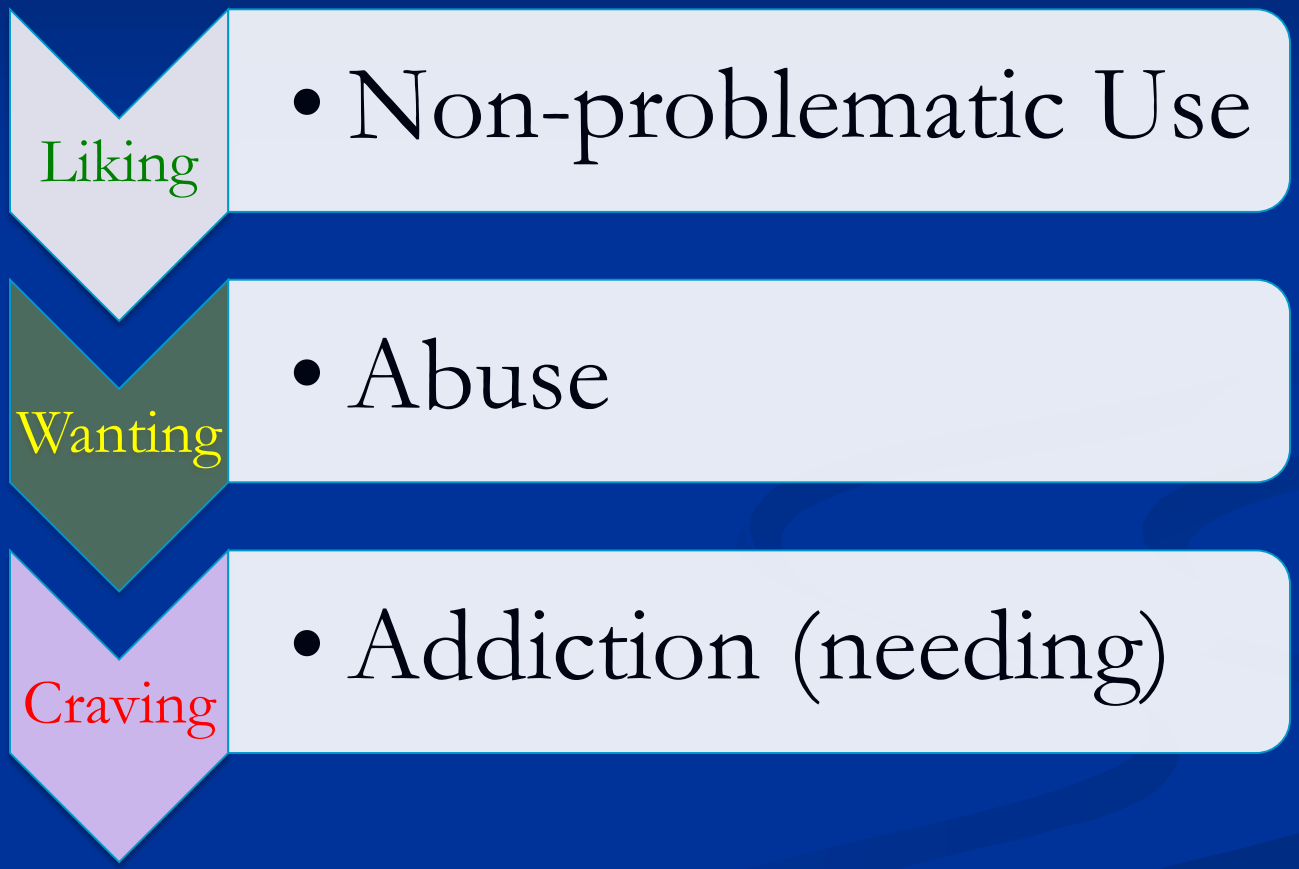




Dr. Merrill Norton
Pharm.D.,D.Ph.,ICCDP-D

Di Chiara and Imperato, PNAS, 1988

Desire Corresponds with Drug Use



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

Withdrawal

- Intensity of withdrawal varies with level and chronicity of use
- Cessation of opioids causes a rebound in functions depressed by chronic use
- First signs occur shortly before next scheduled dose
- Timing influenced by half-life (*fentanyl and heroin have short half-lives.)*
- Peak of withdrawal occurs 36 to 72 hours after last dose
- Acute symptoms subside over 3 to 7 days
- Ongoing symptoms may linger for weeks or months

Withdrawal Symptoms

- Dysphoric mood
- Nausea or vomiting
- Diarrhea
- Tearing or runny nose
- Dilated pupils
- Muscle aches, pain
- Goosebumps, chills
- Sweating
- Yawning
- Fever
- Insomnia

Opioid Use Disorder

- Tolerance*
- Withdrawal*
- More opioid use than intended
- Cravings
- Unsuccessful efforts to cut down
- Spends excessive time in acquisition or recovering from effects
- Activities given up because of opioid use
- Continued use despite consistent social or interpersonal problems
- Failure to fulfill major role obligations
- Recurrent use in hazardous situations
- Continued use despite physical or psychological problems caused by the opioid use

2-3 Mild
4-5 Moderate
6-11 Severe

Definitions

- **Chemical Coping**: Behavior bears a resemblance to addiction because drug-taking is inappropriately used to manage stress or other negative emotions, e.g., depression, anxiety, irritability
- **Substance Abuse**: Any use of a drug for non-therapeutic purposes or use of a drug for purposes other than those for which it is prescribed, often leading to clinically significant impairment or distress (DSM-IV)
- **Misuse**: An unauthorized deviation from the prescription guidelines, generally without intent to "abuse"
- **Diversion**: Use of licit drugs for illicit uses

Taken in part from Portenoy and Payne, 1997; Weissman and Haddox, 1989

Addiction Loop

- Ingestion of opioids creates a euphoric/pleasurable effect.
  - The substance is found to be enjoyable or at least found to reduce other negative conditions
  - Endorphins and enkephalins relieve stress by making you feel warm, safe, fed and loved
  - If you are a trauma survivor these drugs are especially appealing reinforcing the connection between the drug and life's fundamental comforts
- Removal or absence of the substance results in physical and psychological discomfort (withdrawal)
- Opioid agonists must be taken in greater quantities to achieve the same effects (tolerance)
- Chronic use of opioids results in increased perception of pain

Addiction - 5Cs

- Chronic
- Compulsive use
- Control (impaired)
- Craving
- Continued use despite harm

- ***Addiction resides in the person, not the substance***

Opioid Addiction and Trauma

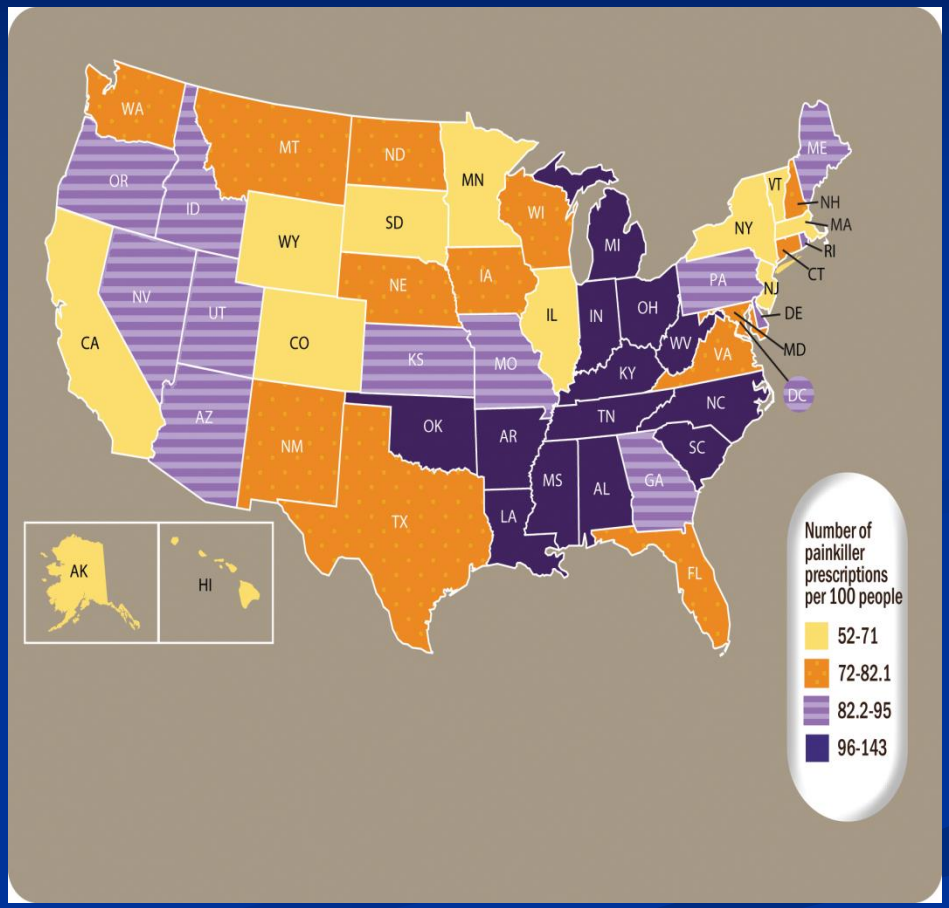
- About 50% of individuals with opioid use disorder have co-occurring conditions:
  - Anxiety, depression and post-traumatic stress disorder are common
  - The more childhood loss and trauma someone has experienced the higher the risk of addiction.
  - Boys who experienced six or more childhood traumas had a 46 times greater risk of becoming an IV user

Relationship Between Prescribed Opioids and Heroin

- 4 in 5 new heroin users started out misusing prescription painkillers.
- Fentanyl-laced heroin is emerging as a national trend.
- In a 2014 survey, 94% of respondents said they chose to use heroin because prescription opioids were (comparatively) too expense and harder to obtain.

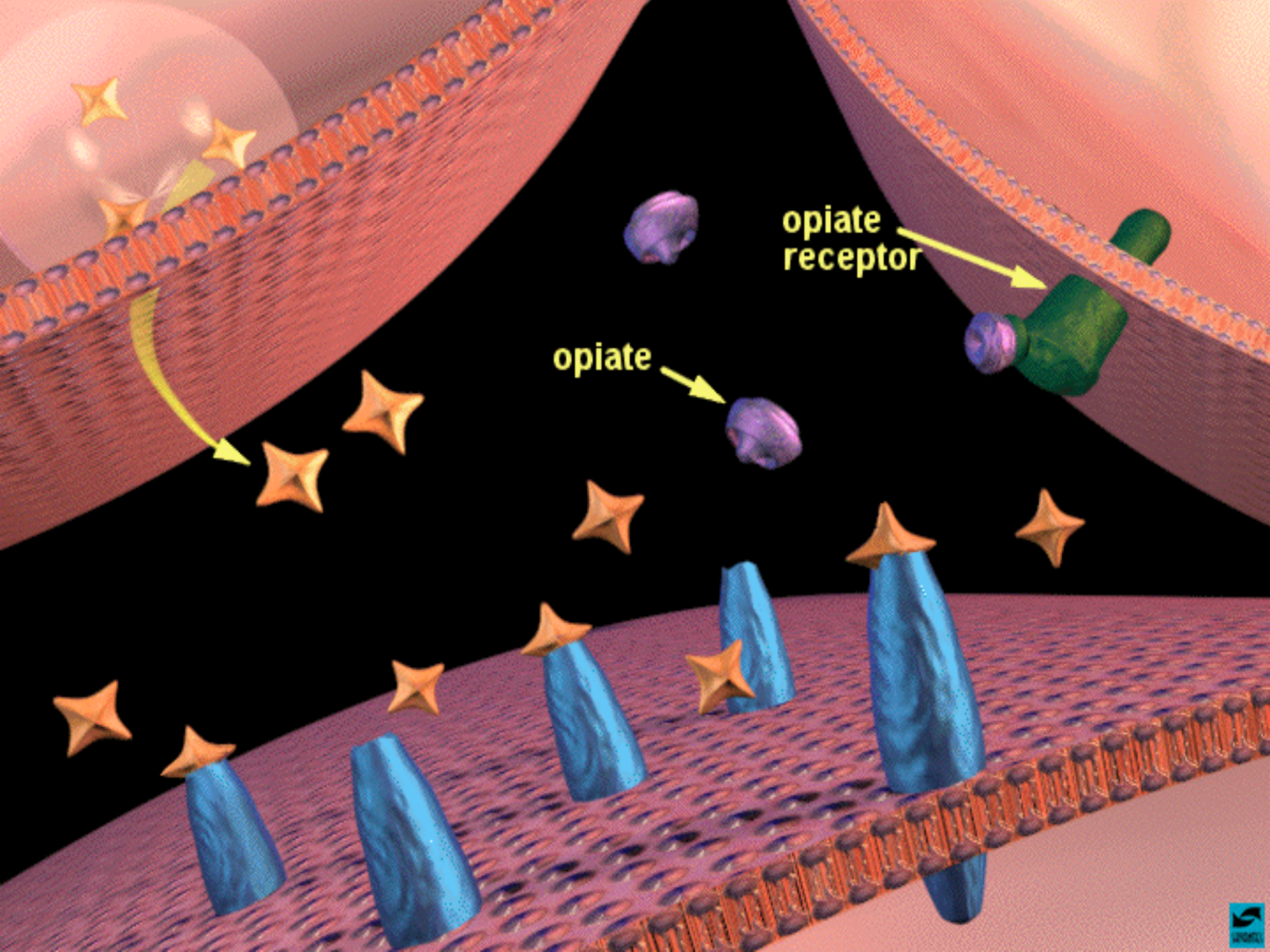
Access to Medications

- The CDC reported that southern states (particularly **Alabama**, **Tennessee**, and West Virginia) had the most painkiller prescriptions per person.
- Nationally, in 2012, providers wrote 259 million prescriptions for painkillers
- In **Alabama,** in 2012, doctors wrote 143 prescriptions for every 100 people.
- States with higher sales per person and more nonmedical use of prescription painkillers tend to have more deaths from drug overdoses.



Opioid Receptors

- Opioids act in the brain by activating mu receptors.
- "Affinity" is the term that means the "strength of the drug binding to the receptor."
  - Buprenorphine, Naltrexone, and Naloxone have high affinity—will displace heroin and methadone
- Once the opioid binds to the receptor it will either activate the receptor (agonist, like Methadone) or not (antagonist, like Naltrexone)


opiate
receptor
opiate

Opioid Antagonists

- Includes Naloxone and Naltrexone
- Occupies the mu receptor without activating
- Does not reinforce with euphoric effects
- Blocks agonist (activating) opioid types

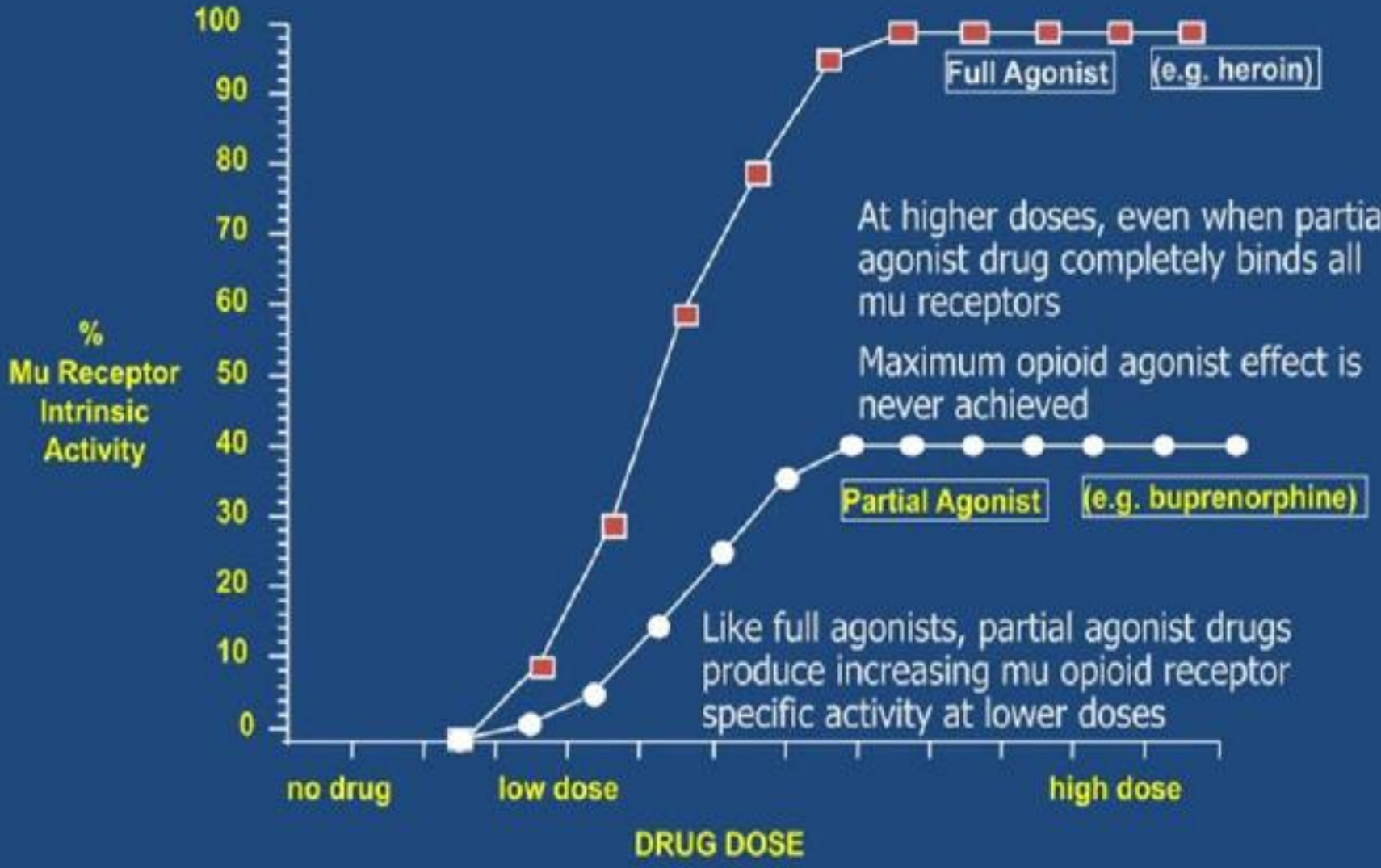
Opioid Agonists

- Include: heroin, codeine, methadone, others
- Activates the mu receptor
- Is highly reinforcing for the person
- Increasing the dose produces increasing mu opioid receptor activity—until maximum receptor activity is reached
- The most misused opioid type

Opioid Partial Agonists

- Includes Buprenorphine
- Activates the receptor at lower levels
- Relatively less reinforcing
- Less commonly misused compared to other opioids

Partial Agonist Activity Levels



Medications for Opioid Use Disorder

- Goal/Definition:
  - The use of medication as prescribed and overseen by a physician knowledgeable about addiction care to support recovery from Substance Use Disorders (SUD).
- Examples:
  - Methadone
  - Buprenorphine
  - Naltrexone

Methadone

- An agonist, the most widely used maintenance agent
- The mainstay of treatment therapy for many years contributing vastly to harm reduction and prevention policies
- Disadvantages:
  - May produce dependence resulting in increased doses with time
  - Subsequent detoxification may be more difficult than from heroin
  - Methadone is a full agonist at mu-opioid receptors and can therefore lead to severe respiratory depression.
  - Dispensed in special clinics where frequent visits are required

Buprenorphine

- A partial agonist at the opioid mu-receptor:
  - Functions on the same brain receptors as morphine—but does not produce high, dependence, or withdrawal syndrome while being prescribed
  - Prevents morphine from binding to opiate receptors, thus blocking its pleasurable effects
  - Blocks withdrawal discomfort by keeping the receptors occupied
- Maximal effects are less than those of full agonists like heroin and methadone, i.e. a "ceiling effect"
  - Lower risk of abuse, dependence and side effects compared to full agonists.
  - Overdose is rare except when combined with benzodiazepines
- Purpose of prescription is to reduce harm—minimize withdrawal symptoms thereby decrease need for continued illicit acquisition.

Advantages of Buprenorphine vs. Methadone:

- Lower level of dependence results from repeated use
- Produces lower subjective euphoric
- A ceiling effect exists for respiratory depressive effects; some reports of reduction in mortality by 10-fold
- More applicable for patients with heart or metabolic illness
- Cited as suitable for home use, can be more easily implemented by outpatient facilities
- Easier termination of medication
  - Withdrawal symptoms are milder compared to methadone

Subutex / Suboxone

- Subutex (buprenorphine)
- Suboxone (buprenorphine plus naloxone)
- When Suboxone is injected intravenously, naloxone is intended to precipitate withdrawal effects in opioid-dependent users to attenuate feelings of "drug liking," and to provide a generally unpleasant experience.
- Buprenorphine and buprenorphine in combination with naloxone both have higher efficacy in study (2003) than placebo.

Detox and Buprenorphine

- Buprenorphine, in some studies, has been shown to be more effective than Clonidine to reduce signs and symptoms of heroin withdrawal
- Gradual dose tapering (28-36 days) appears to be associated with the best outcomes
- Just following detox, a patient is prone to risk for relapse
  - If transferring from methadone, switch to naltrexone is often delayed for up to 14 days due to potential for precipitated withdrawal problems
  - If transferring from buprenorphine, switch to naltrexone can be well tolerated in significantly less time

Naltrexone

- Opioid receptor antagonist
- Non-addictive
- Non-mood altering drug that blocks euphoria from the use of opiates; it has no agonist effects—no opioid subjective effects
- Potential impairment of neuroendocrine function could be assumed with long-term use; however, remarkably few negative effects have been noted in patients taking naltrexone daily for years
- Has also been cited to reduce alcohol cravings
- Injection form (Vivitrol) lasts 28 days; also available in pill form that lasts 24

Detoxification

- The process which eventually leads to achieving a drug-free state through the gradual or abrupt withdrawal of the illicit or prescribed substance.
- Detox schedules are:
  - Labor intensive
  - Require many resources and support for success
- Once detoxed, administration of opioid antagonist (naltrexone) can be used to block the effects of any subsequent opiate use
- Detox alone has limited long-term effectiveness

Goals of Medication in Addiction Treatment

- Restore normal physiology
- Promote psychosocial rehabilitation and non-drug lifestyle
- Reduce symptoms and signs of withdrawal
- Reduce or eliminate craving
- Block effects of alcohol or opioids

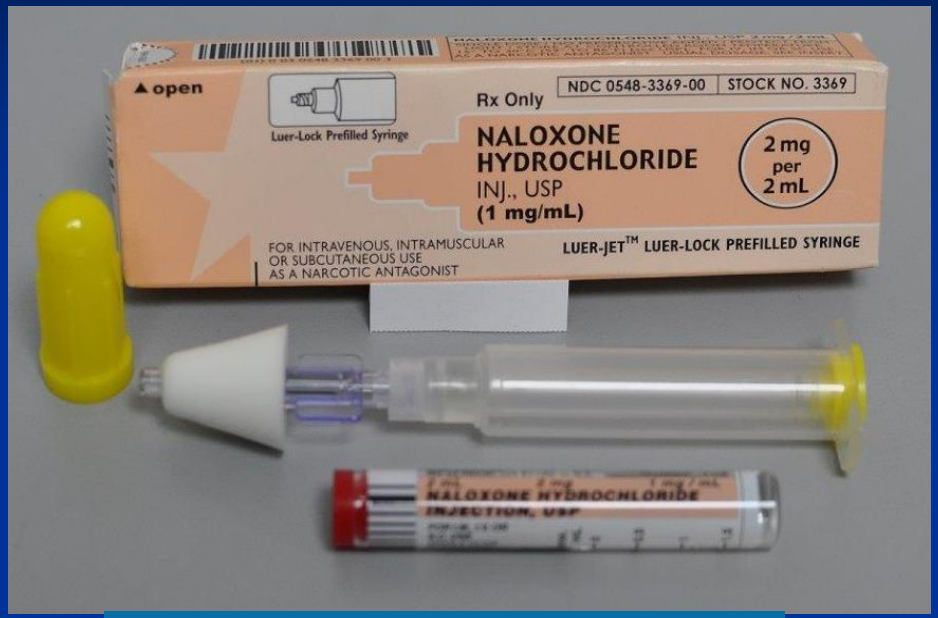
Overdose Prevalence

- Between 1999 and 2014 deaths from pain medication overdoses increased five fold among women while only increasing 3.6 times for men.
- Between 2012 and 2014 Heroin deaths doubled
- Women are more likely than men to be prescribed opioid pain medications and at higher doses
- Of the 18,243 overdose deaths among women in 2014, 71% involved opioid pain medications and 85% involved opioid pain medications and another drug

91 AMERICANS

die every day from an **opioid overdose** (that includes prescription opioids and heroin).

Overdose Reversal Agents



Naloxone

- Designed to rapidly reverse opioid overdose.
- It is an opioid antagonist—it binds to opioid receptors and can reverse and block the effects of other opioids.
- It can very quickly restore normal respiration to a person whose breathing has slowed or stopped as a result of overdosing with heroin or prescription opioid pain medications.
  - EVZIO® is a prefilled auto-injection device that makes it easy for families or emergency personnel to inject naloxone quickly into the outer thigh. Once activated, the device provides verbal instruction to the user describing how to deliver the medication, similar to automated defibrillators.
  - NARCAN® Nasal Spray is a prefilled, needle-free device that requires no assembly and is sprayed into one nostril while patients lay on their back.

Naloxone

- Used to counteract life-threatening depression of the central nervous system and respiratory system.
- Non-scheduled.
- Non-addictive.
- Works only if opioids are present.
- No abuse potential.
- Can be injected or used nasally.
- Wears off in 20 – 90 minutes.

Treatment and Overdose

- Abstinence from opioid use results in an individual's tolerance being lowered
- The majority of overdose deaths are from individuals returning to use within 90 days of leaving treatment or incarceration

Expectations

- Complete full recommended course of treatment, which can include residential care, outpatient care, extended care, etc.
- Take medications as prescribed
- Attend scheduled appointments – medical and therapeutic
- Participate in urine or other drug testing
- Engage family members and other support persons in the recovery process
- Participate in individual therapy and group therapy
- Build a personal recovery program that includes getting a sponsor and becoming actively involved in Alcoholics Anonymous, Narcotics Anonymous, or another community of people in recovery

Treatment Planning

- Share the OUD diagnosis and obtain patient feedback
- Use shared decision-making strategies

*Medication: yes or no

*Which medication?

Where to receive the medication?

What additional services are needed and wanted?

Patients Not Ready to Engage in Treatment

- Provide information on:
    - Reducing injection drug risk
    - Overdose prevention
- Provide Naloxone prescription
- Make appropriate follow up appointments
- Provide resource list

Providers Not Offering Pharmacotherapy

- Focus on medical assessment
- Diagnose OUD
- Discuss treatment options
- Make a treatment referral
- Provide overdose prevention information
- Make a follow up appointment

Providers Offering Pharmacotherapy

- Check PMDP
- Conduct medical, mental health and substance use history
- Current medications
- Physical exam
- Drug testing
- Laboratory tests
- Make diagnosis(DSM-5)

SAMHSA Store

TIP 63

Medications for Opioid Use Disorders