

The Science of Addiction and Its Effective Treatment

Anne Arundel County Opioid Misuse and Overdose
Symposium

April 15, 2015

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JOHNS HOPKINS
M E D I C I N E

Agenda

1. Terminology

- a. Addiction versus Substance Use Disorder
- b. What is a disease?
- c. Neurotransmitter
- d. Opioid vs. opiate

2. A Fast and Furious Overview of Addiction Science

- a. Reward Pathway – It's all about dopamine
- b. Loss of Inhibitory Control – Addiction is a brain disease
- c. Opioid actions in the brain

Agenda

3. Opioid Use Disorder

- a. Etiology
- b. Pathology
- c. Clinical presentation
- d. Time-course (chronic is the norm)

4. Treatment options

- a. Prevention
- b. Methadone and Suboxone™ (buprenorphine)
- c. Naltrexone / Vivitrol™
- d. Psychosocial (inpatient and outpatient)
- e. 12-Step Meetings

Agenda

5. Special Populations

- a. Polysubstance users – it's the norm
- b. MISA
- c. Pregnant women
- d. Chronic pain patients with co-morbid SUD
- e. Inmates

Terminology – Substance Use Disorder (aka addiction)

- **Substance Use Disorder**: a problematic pattern of use of alcohol or other substance that significantly interferes with daily life, and continues despite consequences
- **Addiction (ASAM)**: a compulsive drive to take a drug despite serious adverse consequences

Criteria from the DSM-V for SUD*

2 of more of the following in a 12-month period:

- Taken in larger amounts or over longer period than was intended
- Persistent desire or unsuccessful efforts to cut down / control use
- A great deal of time is spent in activities obtaining, using or recovering from substance use
- Craving / strong desire to use a substance
- Recurrent use resulting in failure to fulfill major role obligations
- Continued use despite recurrent problems associated with use
- Important social, occupational or recreational activities are given up /reduced because of use
- Recurrent use in situations where it is physically hazardous
- Use is continued despite knowledge of having a persistent or recurrent physical or psychological problem that is likely to have been caused or exacerbated by the substance.
- Tolerance
- Withdrawal

***Can be mild, moderate or severe SUD**

Addict, Alcoholic

- Terms originally used by society to refer to patients with SUD but developed pejorative connotation
- Now, used mainly by persons in 12-step programs to identify themselves.
 - “Hello, my name is _____ and I am an addict / alcoholic”

Addiction in Popular Culture

Jack Lemmon • Lee Remick



From the days of wine and roses

DAYS OF WINE AND ROSES



finally comes a night like this.



THE CRITERION COLLECTION

TRAFFIC

MUSIC FROM THE MOTION PICTURE featuring:

Albarn
k
yo
no
der
p
Scream
ed
world

rainspotting



What is a disease?

- **Disease**: abnormal pathological condition that affects all or part of an organism
- 4 Aspects
 - Etiology
 - Pathogenesis
 - Morphologic changes
 - Clinical significance

Diabetes vs. Addiction – Both diseases!!

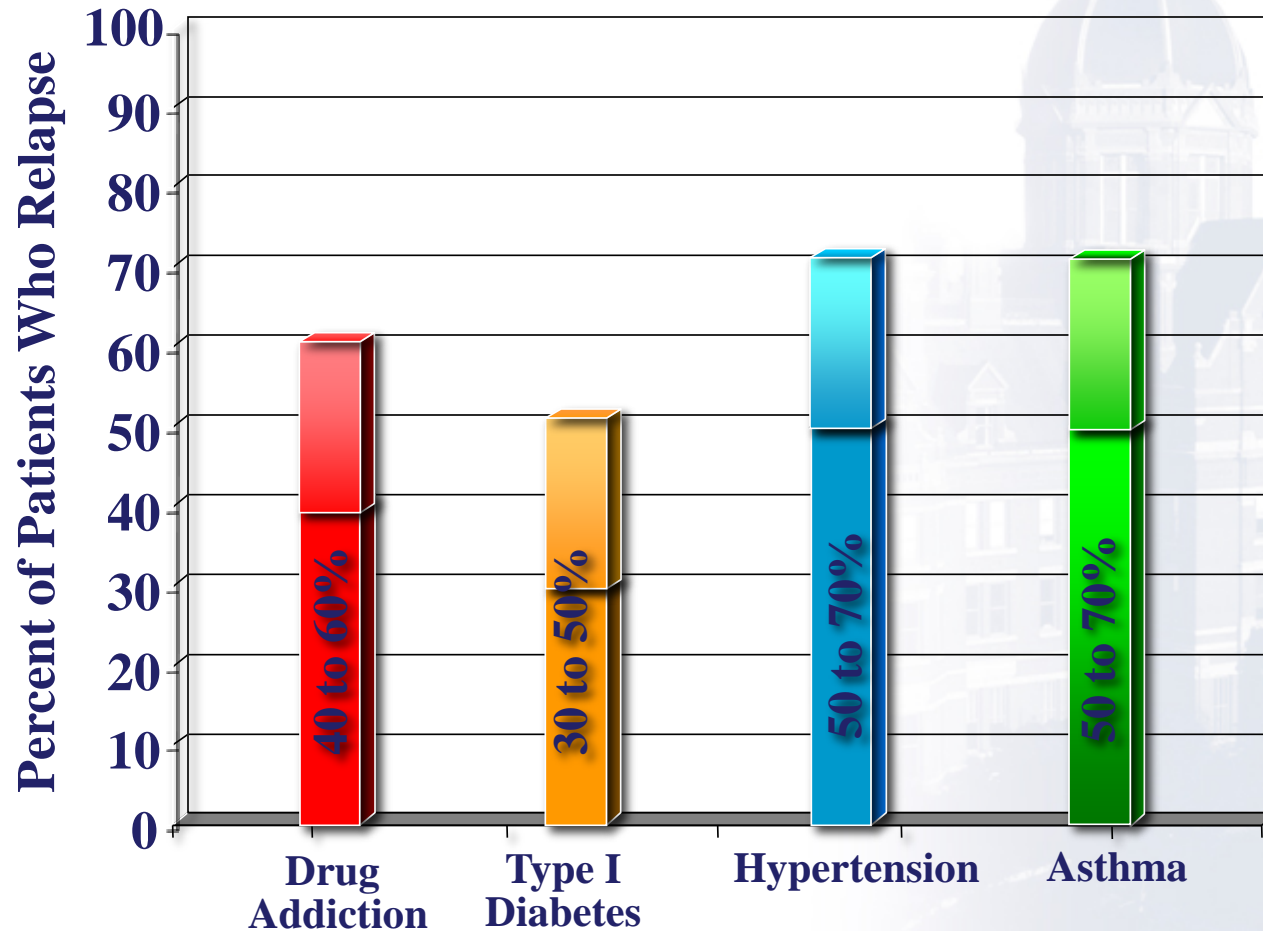
Type I Diabetes

- Etiology: autoimmune destruction of pancreas
- Pathogenesis: Death of Beta Islet cells over time (only cells that produce insulin)
- Morphologic changes: increase in inflammation and evidence of cell death. Loss of plasma insulin.
- Clinical presentation: very high blood sugar, coma, death, etc.
- CHRONIC

Addiction

- Etiology: genetic predisposition, early life experiences and exposure to substance.
- Pathogenesis: change in reward (dopamine) pathways in the brain.
- Morphologic changes: increase in dopamine release in key brain areas; changes in opioid receptor density, changes in neuron connections and ability to respond to brain signaling
- Clinical presentation: problematic substance use, tolerance, withdrawal, etc.
- CHRONIC

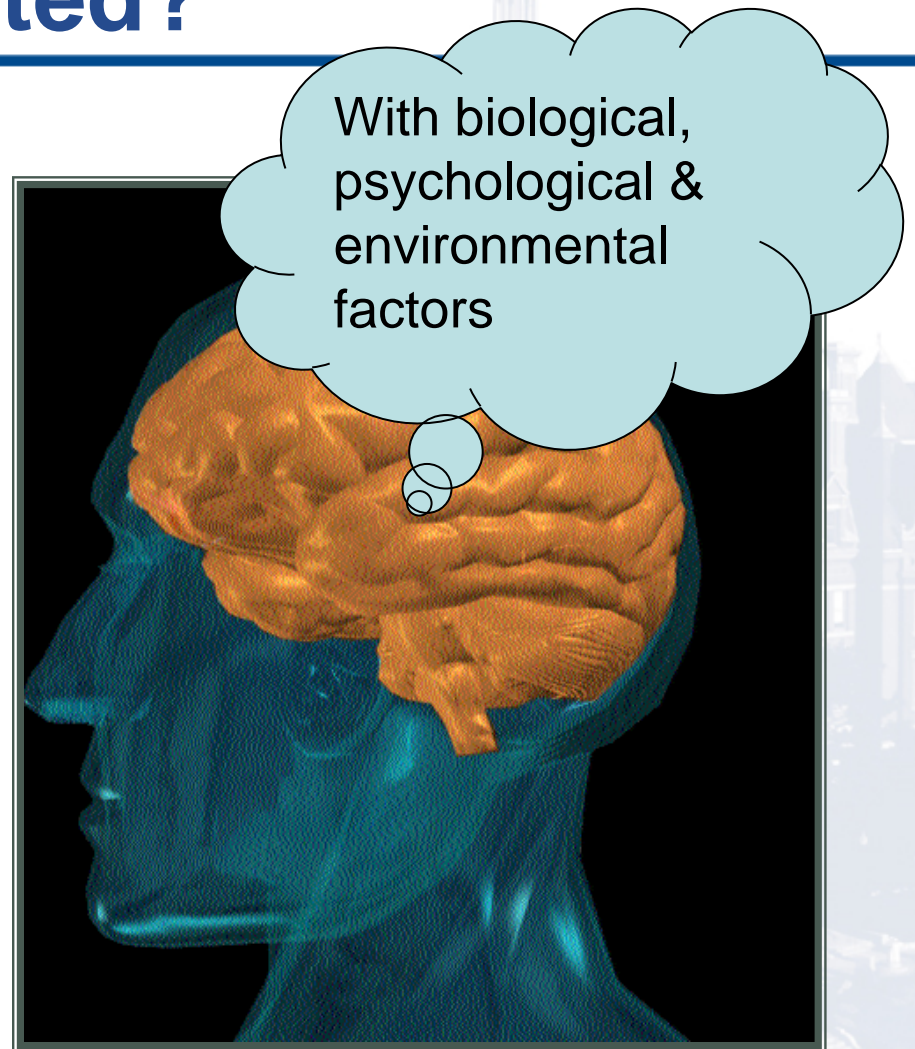
Relapse Rates are Similar for SUD and Other Chronic Illnesses



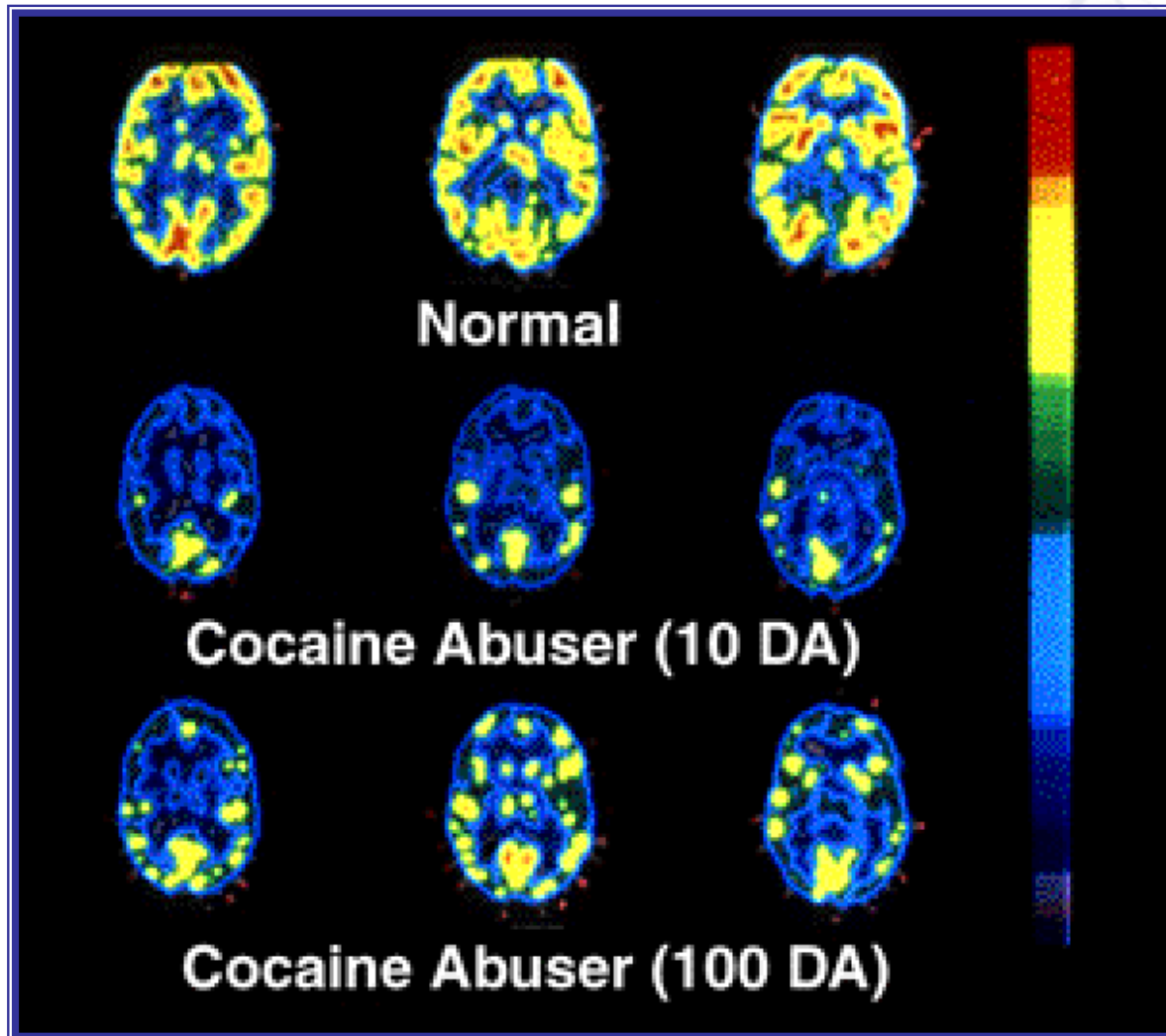
McLellan et al., JAMA, 2000.

If SUDs are diseases, what part of the body is affected?

- Addiction / SUD is a brain disease

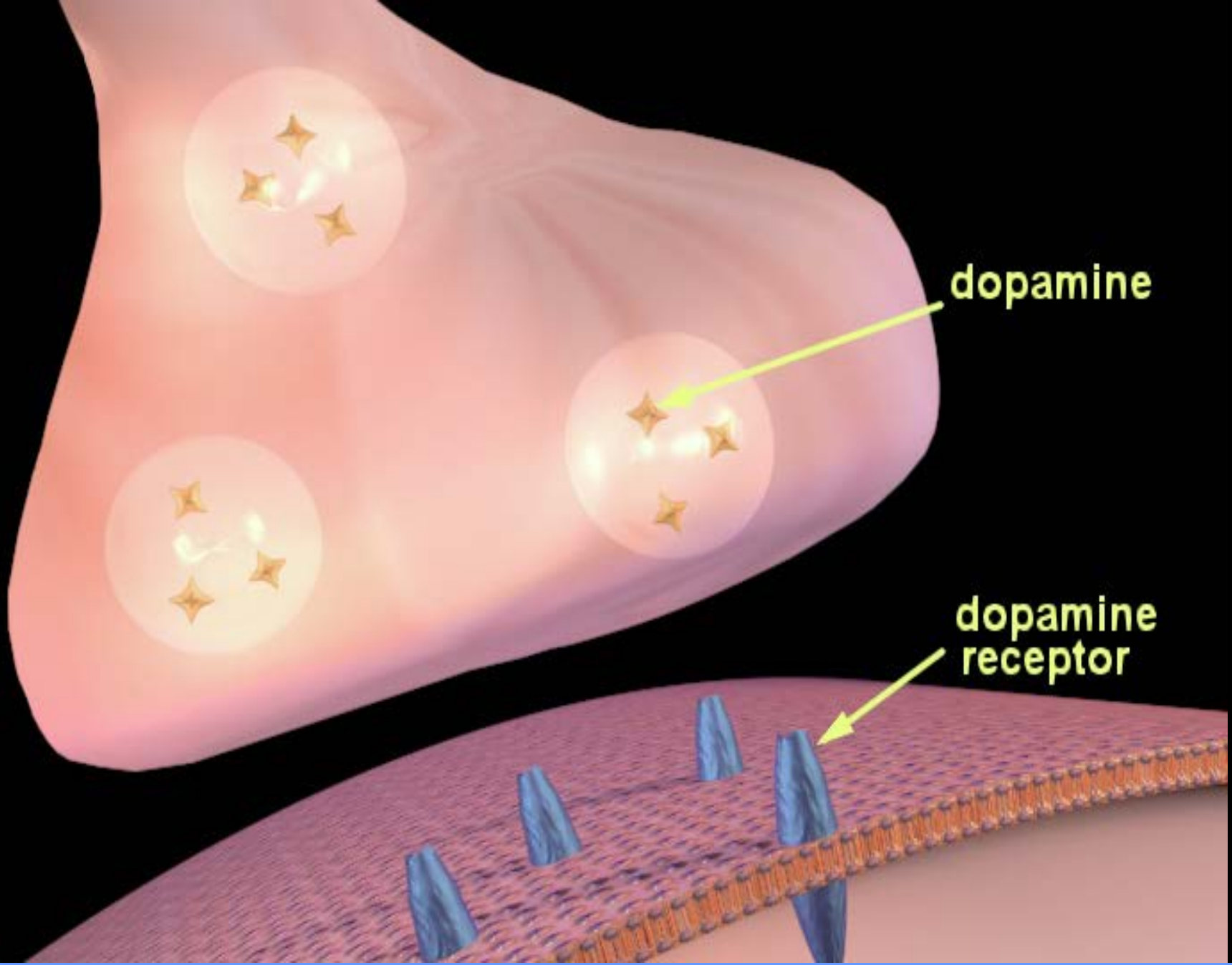


Normal Brain Function versus Brain after Chronic Cocaine Use



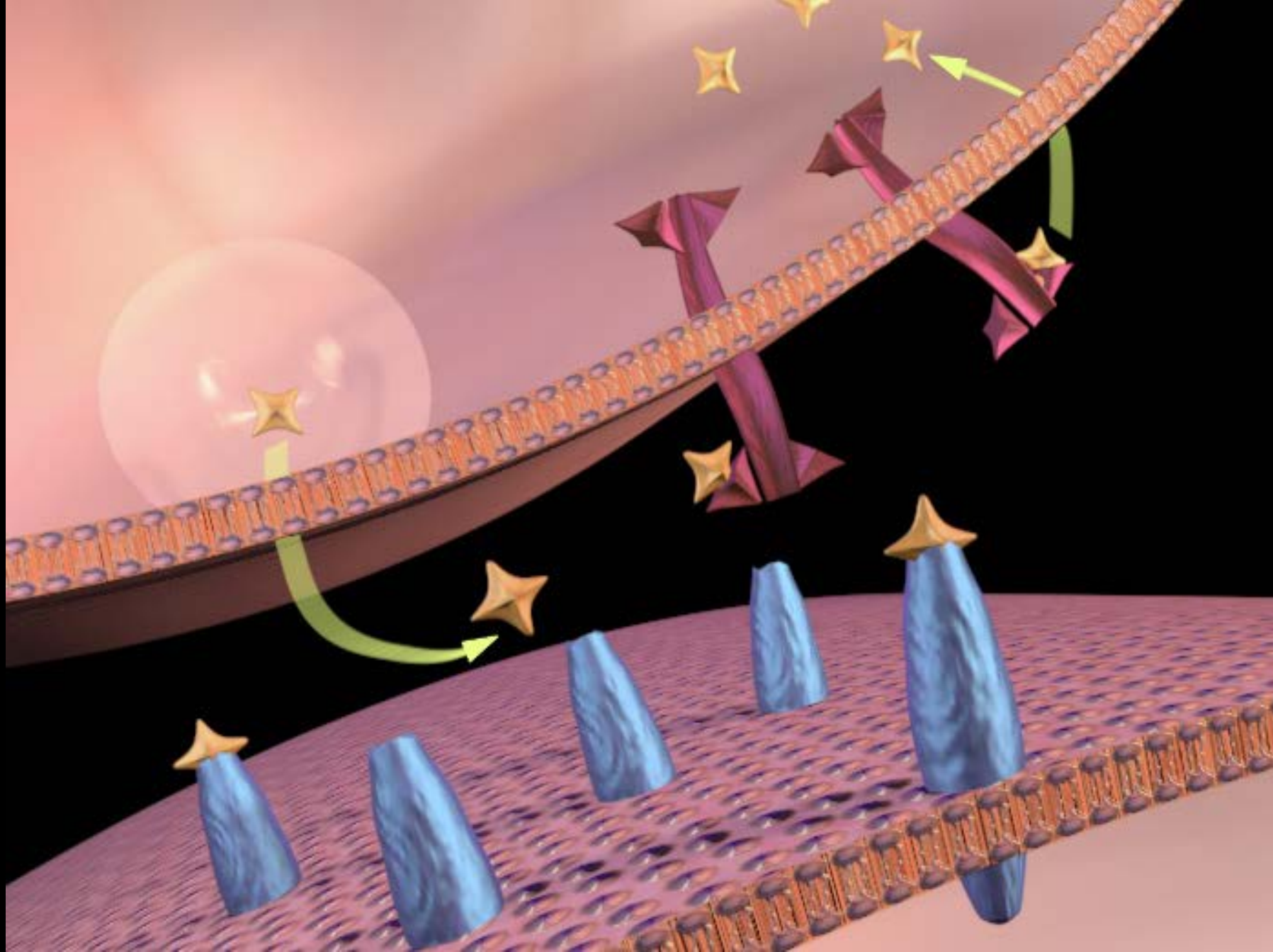
Neurotransmitter

- A chemical that allows neurons in the brain to communicate with each other.
- A NT is like a key and is released from the end of a neuron and this attaches to its lock (a receptor) on the adjacent neuron
- Dopamine is a NT that can cause pleasure when released in certain brain areas. Release controlled by other NT (GABA, endorphins)

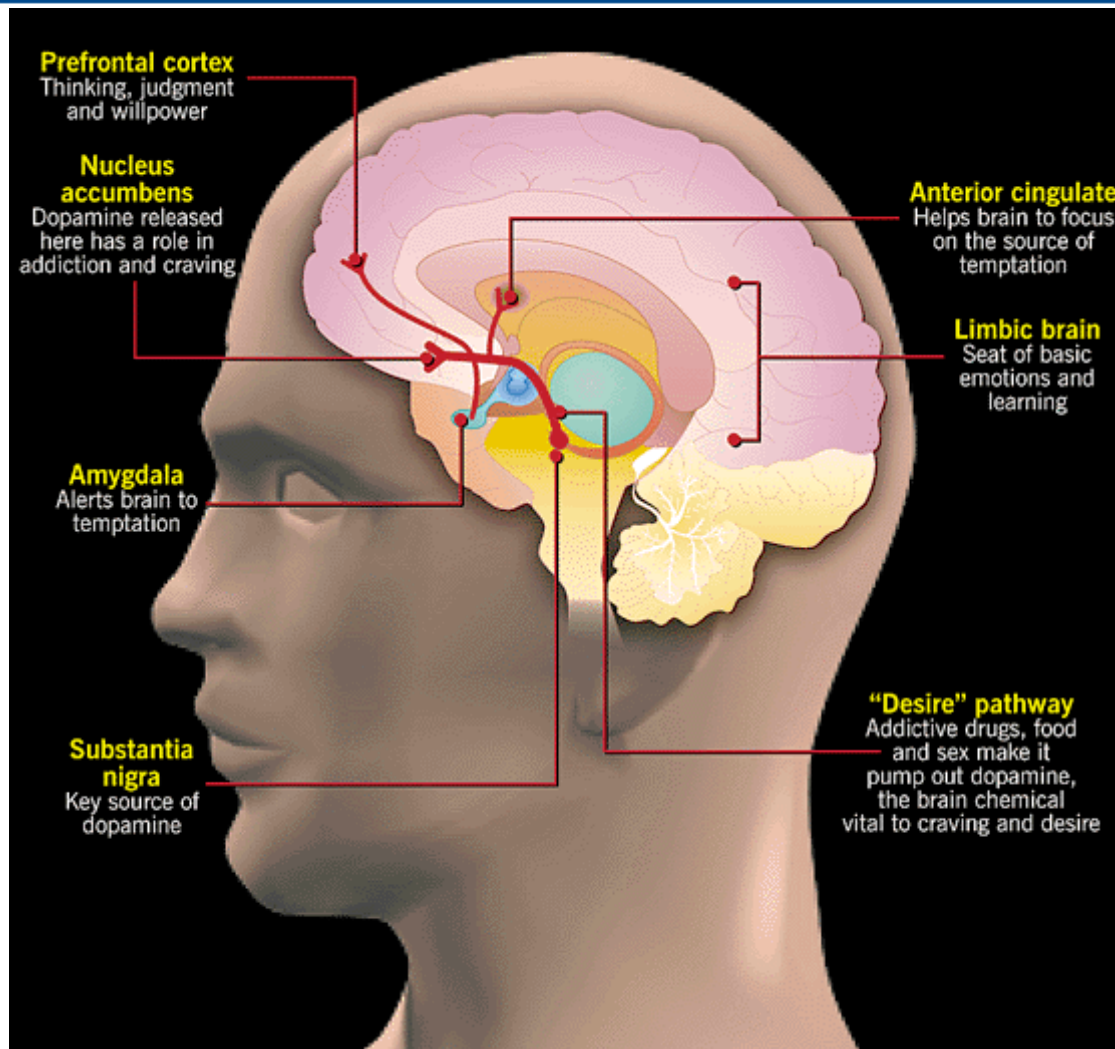


dopamine

dopamine
receptor



This is Your Brain



This is your Brain on Drugs

Dopamine D2 Receptors are Lower in Addiction



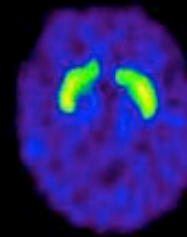
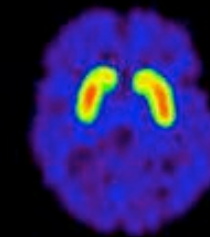
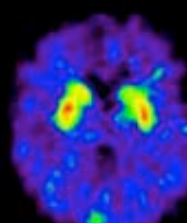
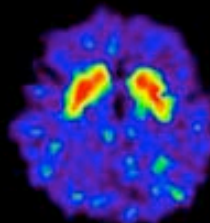
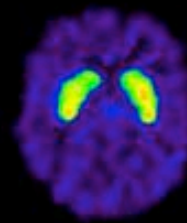
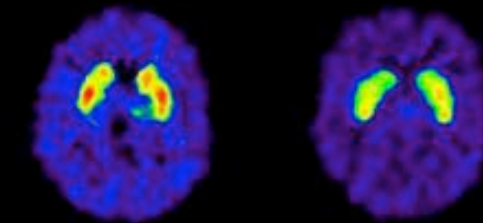
Cocaine



Alcohol



Heroin



control

addicted

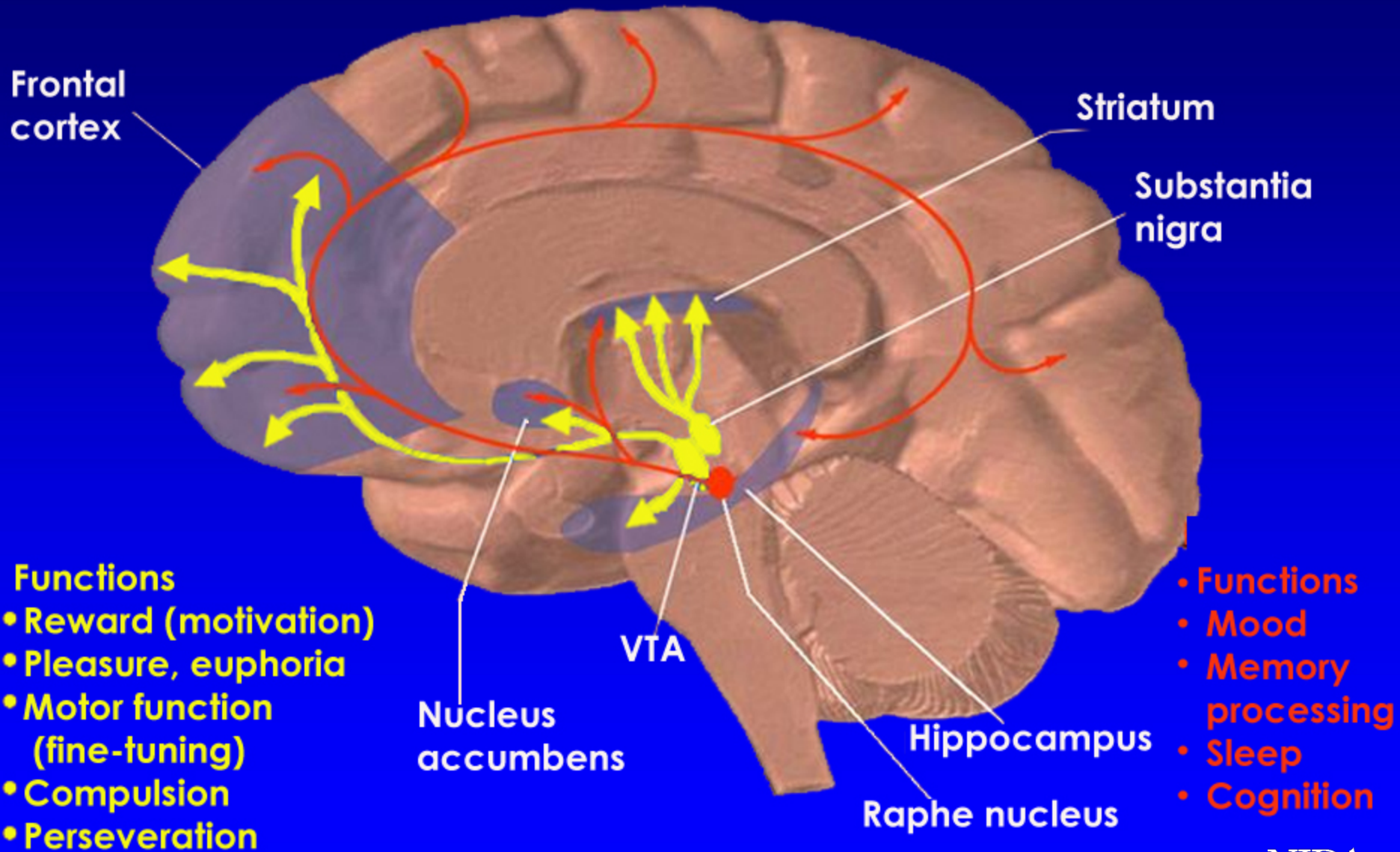


But Dopamine is Only Part of the Story

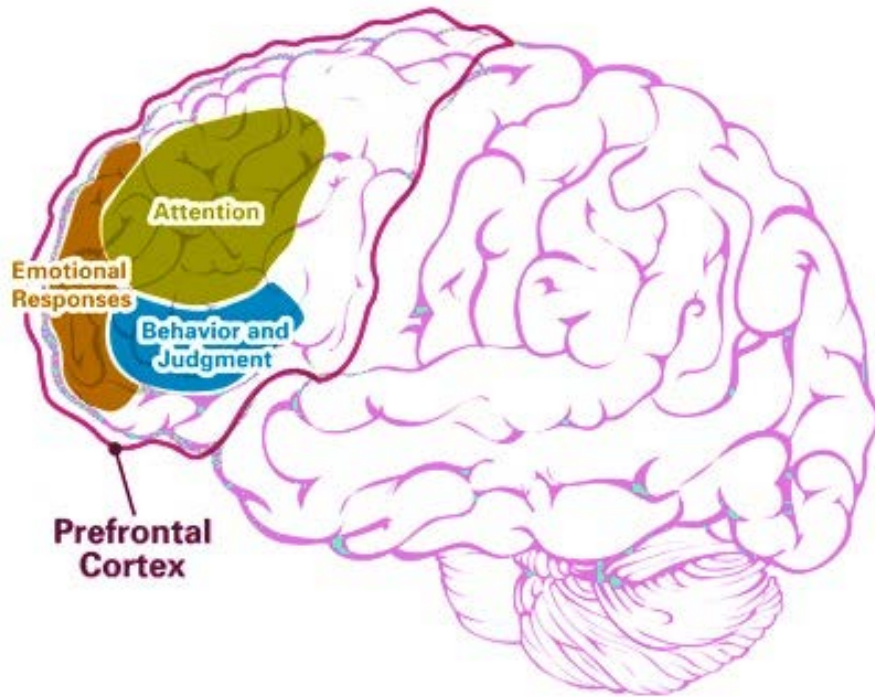
- Scientific research has shown that other neurotransmitter systems are also affected:
 - Serotonin
 - Regulates mood, sleep, etc.
 - Glutamate
 - Regulates learning and memory, etc.
 - Endogenous opioids

Dopamine Pathways

Serotonin Pathways



Loss of Inhibitory Control



- Inhibitory control develops at later stage then reward pathways (late adolescence / early adulthood)
- Located in the Prefrontal cortex
- Dopamine and

Opioids vs. Opiates

- Narcotic (a stupor-inducing drug)
- Function as analgesics and reduce pain sensitivity
- Two technical categories:
 - Opiates: Derivatives of opium
 - Opioids: Refers to any drug that activates the opioid receptors (refers to synthetic opioids)
- Bind to opioid receptors throughout the body

Poppy Fields – You aren't in Kansas any More



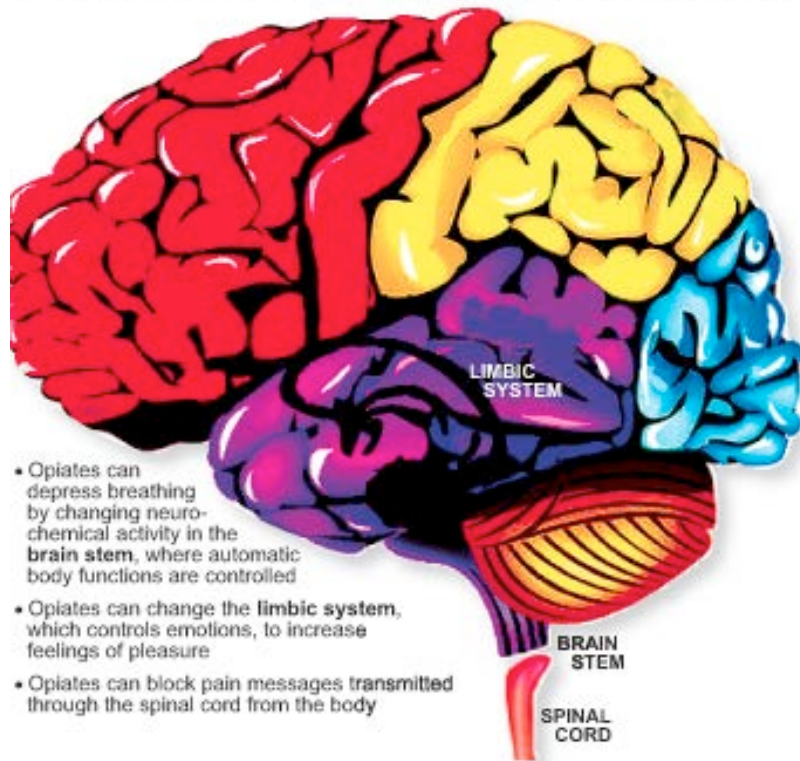
papaver somniferum

Endogenous opioids

- The human body produces 3 major types of endogenous opioids (NT)
 - Endorphins
 - Enkephalins
 - Dynorphins
- Function in regulating stress response, analgesia, euphoria during sex, appetite, body temperature,

Opioid Receptors in the Brain

OPIATES
ACT ON MANY PLACES IN THE BRAIN AND NERVOUS SYSTEM



- Four subtypes – mu, kappa, delta, and ORL-1
- Receptors, when an **agonist** binds, function to block neurotransmission (e.g., block pain signaling)

Heroin

- Diacetylmorphine was first synthesized in 1874 and sold by Bayer under the trade name Heroin
 - Heroin is from the German word *heroisch*- meaning heroic
- Developed to treat morphine and codeine dependence
- 2 acetyl groups make it very lipid soluble (it crosses the blood-brain-barrier very quickly)
 - This makes it 10x more potent than morphine
- Physicians believed heroin was a safe alternative to these drugs because it was “not habit producing”.

Heroin



- US heroin is primarily from South America (Columbia, Venezuela), although heroin from Afghanistan is increasing
 - Street purity of heroin has increased from 4-6% (1970' s/1980' s) to 27-46%.
 - Users can now snort or smoke heroin, as well as inject it.
- Different types of heroin available:
 - Black Tar Heroin: Mexican heroin.
 - Cheese Heroin: New drug of abuse. Very toxic. Black tar heroin mixed with diphenhydramine (Benadryl)

Synthetic Opioids / Prescription analgesic medications

Abused Pharmaceutical Substances

National Association of Drug Diversion Investigators, Inc.
 1-888-39NADDI www.naddi.org

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<p>Alprazolam [Ⓢ]</p> <p><i>Xanax</i>[®]</p> <p>0.25 mg</p> <p>0.5 mg</p> <p>1 mg</p> <p>2 mg</p>	<p>Carisoprodol ^{RX}</p> <p><i>Soma</i>[®]</p> <p>350 mg</p> <p>Soma Compd w/Codine [Ⓢ]</p> <p><i>carisoprodol/aspirin/codine</i></p> <p>200 mg/ 325 mg/ 16 mg</p>	<p>Hydrocodone/ Acetaminophen [Ⓢ]</p> <p><i>Lorced</i>[®]</p> <p>5 mg/ 500 mg</p> <p>7.5 mg/ 650 mg</p> <p>10 mg/ 650 mg</p> <p><i>Lortab</i>[®]</p> <p>5 mg/ 500 mg</p> <p>7.5 mg/ 500 mg</p> <p>10 mg/ 500 mg</p> <p><i>Norco</i>[®]</p> <p>7.5 mg/ 325 mg</p> <p>10 mg/ 325 mg</p> <p><i>Vicodin</i>[®]</p> <p>5 mg/ 500 mg</p> <p>10 mg/ 660 mg</p> <p>7.5 mg/ 750 mg</p>	<p>Hydrocodone/ Acetaminophen [Ⓢ]</p> <p><i>Generic</i></p> <p>10 mg/ 325 mg</p> <p>7.5 mg/ 750 mg</p> <p>10 mg/ 650 mg</p> <p>10 mg/ 660 mg</p> <p>10 mg/ 325 mg</p> <p>10 mg/ 325 mg</p> <p>7.5 mg/ 500 mg</p> <p>7.5 mg/ 500 mg</p> <p>10 mg/ 500 mg</p> <p>10 mg/ 650 mg</p> <p>5 mg/ 500 mg</p> <p>7.5 mg/ 750 mg</p>	<p>Hydromorphone [Ⓢ]</p> <p><i>Dilaudid</i>[®]</p> <p>1 mg</p> <p>2 mg</p> <p>3 mg</p> <p>4 mg</p> <p>8 mg</p> <p><i>Generic</i></p> <p>2 mg</p> <p>4 mg</p> <p>8 mg</p> <p>2 mg</p> <p>4 mg</p>	<p>Methadone [Ⓢ]</p> <p>5 mg</p> <p>5 mg</p> <p>10 mg</p> <p>10 mg</p> <p>10 mg</p> <p>5 mg</p> <p>10 mg</p> <p>40 mg</p> <p>40 mg</p> <p>40 mg</p>	<p>Morphine [Ⓢ]</p> <p><i>MS Contin</i>[®]</p> <p>15 mg</p> <p>30 mg</p> <p>60 mg</p> <p>100 mg</p> <p>200 mg</p> <p><i>Oxazepam</i> [Ⓢ]</p> <p><i>Serax</i>[®]</p> <p>15 mg</p> <p>10 mg</p> <p>15 mg</p> <p>30 mg</p>	<p>Oxycodone/ Acetaminophen [Ⓢ]</p> <p><i>Percocet</i>[®]</p> <p>2.5 mg/ 325 mg</p> <p>5 mg/ 325 mg</p> <p>7.5 mg/ 325 mg</p> <p>7.5 mg/ 500 mg</p> <p>10 mg/ 325 mg</p> <p>10 mg/ 650 mg</p> <p><i>Tylox</i>[®]</p> <p>5 mg/ 500 mg</p>	<p>Pentazocine/Naloxone [Ⓢ]</p> <p><i>Talwin NX</i>[®]</p> <p>50 mg/ 0.5 mg</p> <p><i>Generic</i></p> <p>50 mg/ 0.5 mg</p>	<p>Phentermine [Ⓢ]</p> <p><i>Adipex-P</i>[®]</p> <p>37.5 mg</p> <p>37.5 mg</p> <p><i>Fastin</i>[®]</p> <p>30 mg</p> <p><i>Ionamin</i>[®]</p> <p>15 mg</p> <p>30 mg</p>	<p>Propoxyphene/ Acetaminophen [Ⓢ]</p> <p><i>Durvyocet-N</i>[®]</p> <p>50 mg/ 325 mg</p> <p>100 mg/ 650 mg</p>	<p>Oxycodone [Ⓢ]</p> <p><i>OxyContin</i>[®]</p> <p>10 mg</p> <p>20 mg</p> <p>40 mg</p> <p>80 mg</p> <p>160 mg</p> <p>Oxycodone HCl/Aspirin [Ⓢ]</p> <p><i>Percodan</i>[®]</p> <p>4.5 mg/ 325 mg/ 0.38 mg</p> <p>2.25 mg/ 325 mg/ 0.19 mg</p>	<p>Oxycodone Terephthadate [Ⓢ]</p> <p><i>Generic</i></p> <p>10 mg</p> <p>20 mg</p> <p>40 mg</p> <p>80 mg</p> <p>160 mg</p> <p>Pentazocine/ Acetaminophen [Ⓢ]</p> <p><i>Talacen</i>[®]</p> <p>25 mg/ 650 mg</p>	<p>Methylphenidate [Ⓢ]</p> <p><i>Ritalin</i>[®]</p> <p>5 mg</p> <p>10 mg</p> <p>20 mg</p> <p>20 mg</p> <p>20 mg</p> <p><i>Generic</i></p> <p>5 mg</p> <p>10 mg</p> <p>20 mg</p>	<p>Lorazepam [Ⓢ]</p> <p><i>Ativan</i>[®]</p> <p>0.5 mg</p> <p>1 mg</p> <p>2 mg</p>	<p>Meperidine [Ⓢ]</p> <p><i>Demerol</i>[®]</p> <p>50 mg</p> <p>100 mg</p>	<p>Pentazocine/Aspirin [Ⓢ]</p> <p><i>Talwin Compound</i>[®]</p> <p>12.5 mg/ 325 mg</p>	<p>Triazolam [Ⓢ]</p> <p><i>Halcion</i>[®]</p> <p>0.125 mg</p> <p>0.25 mg</p>	<p>Benzphetamine [Ⓢ]</p> <p><i>Didrex</i>[®]</p> <p>50 mg</p>	<p>Dextroamphetamine [Ⓢ]</p> <p><i>Dexedrine</i>[®]</p> <p>5 mg</p> <p>10 mg</p> <p>15 mg</p>	<p>Diazepam [Ⓢ]</p> <p><i>Valium</i>[®]</p> <p>2 mg</p> <p>5 mg</p> <p>10 mg</p>	<p>Fentanyl [Ⓢ]</p> <p><i>Duragesic</i>[®]</p> <p>5 mg</p> <p>(Also available in 2.5, 7.5, and 10 mg doses)</p>	<p>Butorphanol Tartrate [Ⓢ]</p> <p><i>Stadol</i>[®]</p> <p>10 mg/ml</p>	<p>Amphetamine Mixture [Ⓢ]</p> <p><i>Adderall</i>[®]</p> <p>5 mg</p> <p>7.5 mg</p> <p>10 mg</p> <p>12.5 mg</p> <p>15 mg</p> <p>20 mg</p> <p>30 mg</p> <p>10 mg</p> <p>20 mg</p> <p>30 mg</p>	<p>Clonazepam [Ⓢ]</p> <p><i>Klonopin</i>[®]</p> <p>0.5 mg</p> <p>1 mg</p> <p>2 mg</p>	<p>Codine/ Acetaminophen [Ⓢ]</p> <p><i>Tylenol w/Codine</i>[®]</p> <p>15 mg/ 300 mg</p> <p>30 mg/ 300 mg</p> <p>60 mg/ 300 mg</p>
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Opioid Use Disorder (OUD)

- a compulsive drive to take opioids despite serious adverse consequences



CRAIG SWANSON © WWW.PERSPICUITY.COM

- OUD is a disease with:
 - Etiology
 - Pathogenesis
 - Morphologic changes
 - Clinical significance

Etiology

- Most people who go on to develop OUD, start use in adolescence.
- Now, significant numbers also start with legitimate prescription for opioid analgesics
- Risk factors include:
 - Family History
 - Co-morbid psychiatric illness
 - Co-morbid drug / alcohol use disorder
 - Early childhood sexual / physical abuse
 - Sex (Men > Women)
 - Opioid availability
 - Peer groups



Pathogenesis

- Initially, patients use for euphoria (feel “high”) or to “feel better”
- Then, patients transition to use opioids to prevent withdrawal OR use higher amounts to receive same effect (tolerance)
- The rising and falling of opioid in the patient’s bloodstream is important

Clinical Presentation of Opioid Withdrawal

- **Initial Phase:**
 - Time course is dependent on half-life of specific opioid
 - Constellation of symptoms include:
 - Physiologic: nausea, vomiting, diarrhea, tachycardia, elevated blood pressure, sweating, gooseflesh, insomnia, and dilated pupils
 - Psychological: anxiety, dysphoria
 - Hyperalgesia: muscle and joint pain
- **Protracted abstinence (Controversial)**
 - Early studies showed “Altered physiological function” lasting for up to 6 months
 - Insomnia is a large component!

Morphological Changes in persons with OUD

- Opioid receptors
 - Decreased amount in brain
 - Not as responsive to endogenous or exogenous opioids
- Brain activity – a “new set point”
 - The brain “resets” itself in order to function normally in the presence of high levels of opioids (which normally block / slow down neurotransmission).

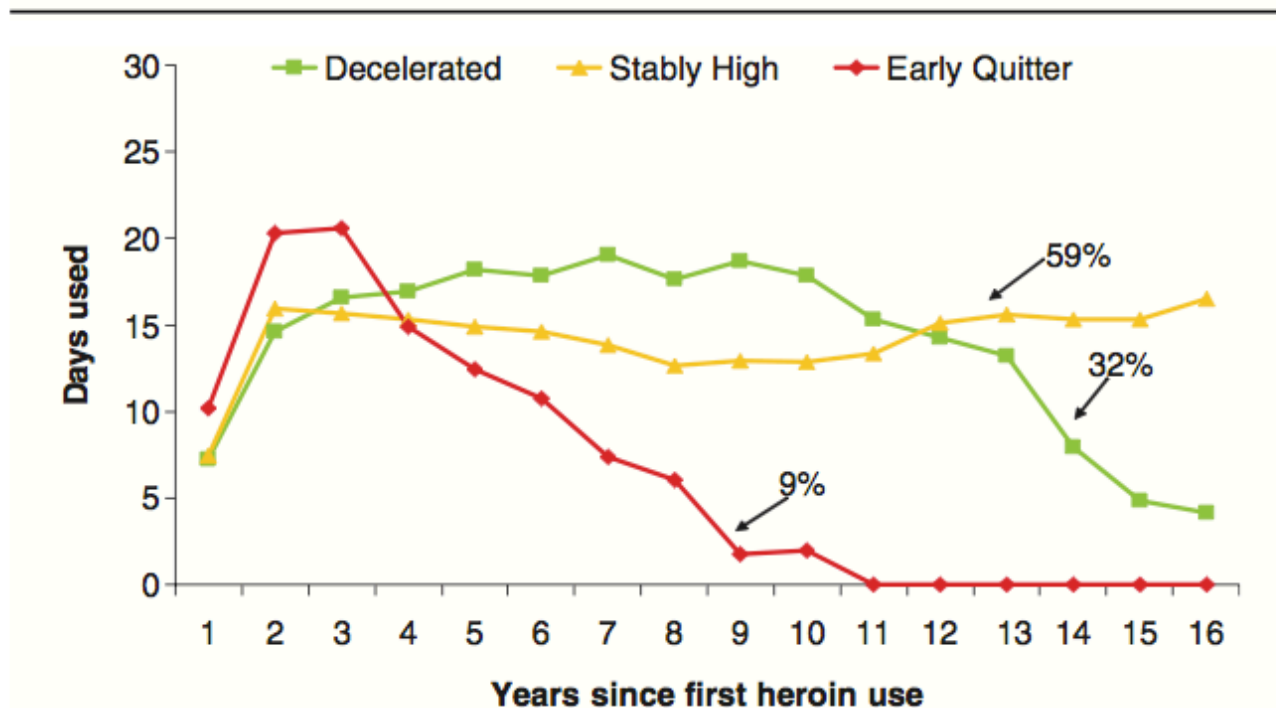
Clinical Significance

- Use of DSM-V criteria to help establish diagnosis of OUD
- Utilize urine drug screens to have objective marker of recent opioid use
- Use of standardized measures to measure withdrawal symptoms
- OUD associated with large health risks, including suicide, HIV, psychiatric illness, and **overdose.**

Natural History of Opioid Addiction

- Opioid users enter treatment an average of 8 times before staying abstinent.

Days Using Heroin: A 33-Year Follow-Up



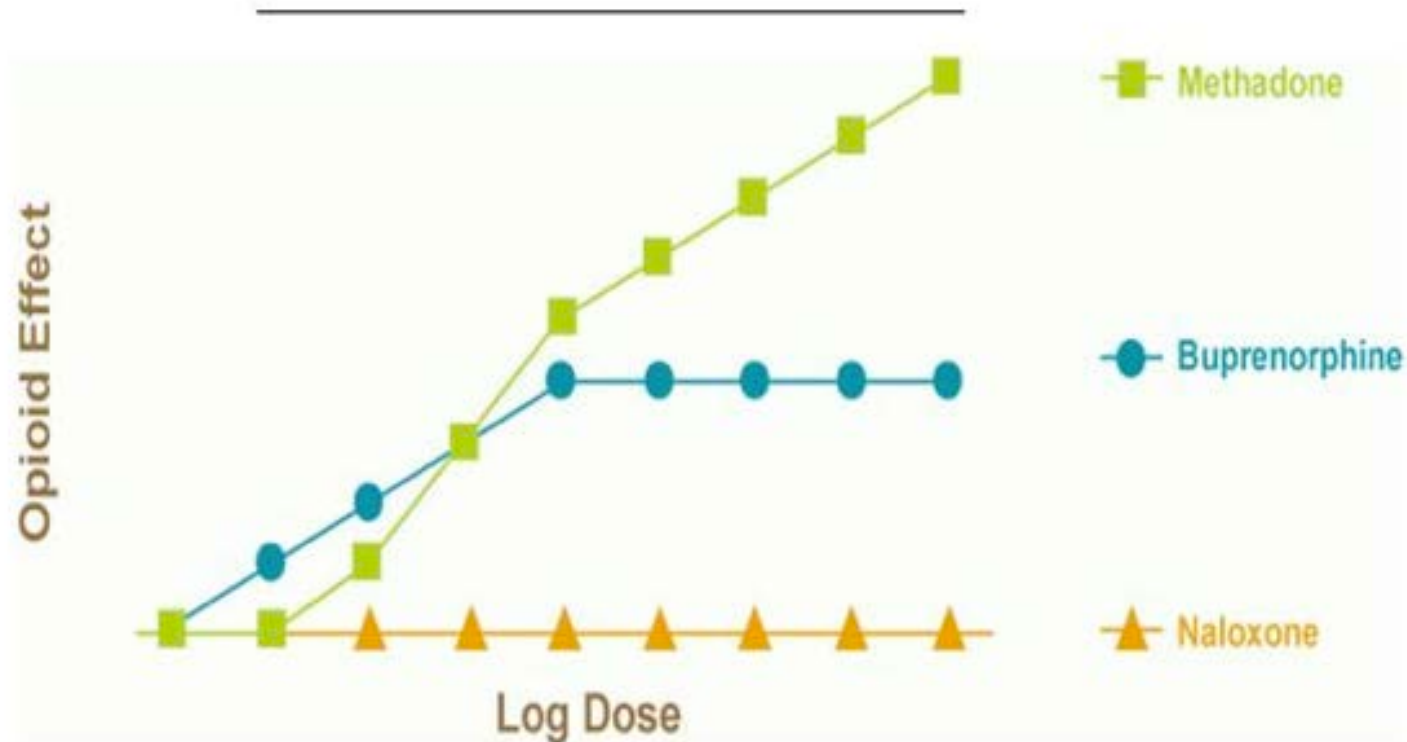
There is Hope: Treatment does work!!



Detoxification does not work for the Majority of People

- Higher rates of completion of inpatient medical detoxification compared with outpatient care. (Day and Strang, 2011)
- Vast majority (>80%) of individuals relapse to opioid use within the next year, most within the first 2 months. (Northrup et al., 2015)
- Recommendation is now for long-term maintenance therapy for OUD (>12 months)

Agonist, Partial Agonist, Antagonist Effects



Agonist Replacement Therapy

- If the brain now needs an opioid to function normally, why not provide a replacement opioid agonist that is
 - Less likely to make a person high
 - Needs to be taken once a day or less
 - Physicians are legally allowed to prescribe
 - Has favorable safety profile
- But, fixing the brain chemistry is not the only treatment needed by persons with OUD

Methadone

- Showed to be effective for reduction in opioid use, retaining people in treatment, and improvement in psychosocial functioning since 1960s.
- Full mu opioid receptor agonist
- Used for OUD only in federally licensed treatment centers
- Patients come to clinic daily for medication, and staff provide psychosocial interventions



Buprenorphine (Suboxone™, Subutex™)

- Only current medication allowed to be dispensed by qualified physicians for the treatment of OUD in outpatient clinic
- Partial agonist, usually combined with low dose naltrexone to prevent abuse
- Better safety profile than methadone
- No psychosocial intervention routinely provided.
- Similar efficacy as methadone for treatment retention and stopping illicit opioid use



Naltrexone

- Opioid antagonist
- Blocks the ability of opioid to bind to receptor and produce positive effects (“high”)
- Available in once daily pill form (Revia™) or once monthly depot injection (Vivitrol™)
- Also used to treat alcohol use disorders.



Psychosocial (drug-free) treatments

- Long-term Residential / Therapeutic communities
- Intensive Outpatient
- Outpatient drug-free
- Short term inpatient (28 days or less)
- Few controlled comparisons to opioid maintenance treatment.
- LTR is associated with reductions in drug-use and achieving/maintaining abstinence.
- Leaving TC is associated with increased risk for relapse
- >6 months of treatment is usually needed

Narcotics Anonymous

- 12-step therapy
- Groups are independent
- Persons with OUD work with each other to achieve and maintain abstinence.
- Very little evidence from controlled studies showing efficacy as sole treatment modality
- Can increase odds of abstinence in those attending while undergoing other treatments

Special Populations

- Polysubstance use –
It is the norm
 - Require additional treatment to stop other drug / alcohol use
- OUD patients often have co-morbid mental illness.
 - Dual diagnosis treatment is needed
- Pregnant women
 - Agonist treatment is safe and effective
- Co-morbid chronic pain
 - Additional studies are needed.
- Incarcerated adults
 - Starting / continuing maintenance therapy can help reduce recidivism
- Adolescents
 - Buprenorphine is approved for patients 16+
 - Methadone is only approved for 18+

Thank you! Any questions?

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Frankly, my dear, I know treatment works!