

UCLA-SAPC Lecture Series  
March 13, 2015



# Medication-Assisted Treatment

## Overview and Evidence

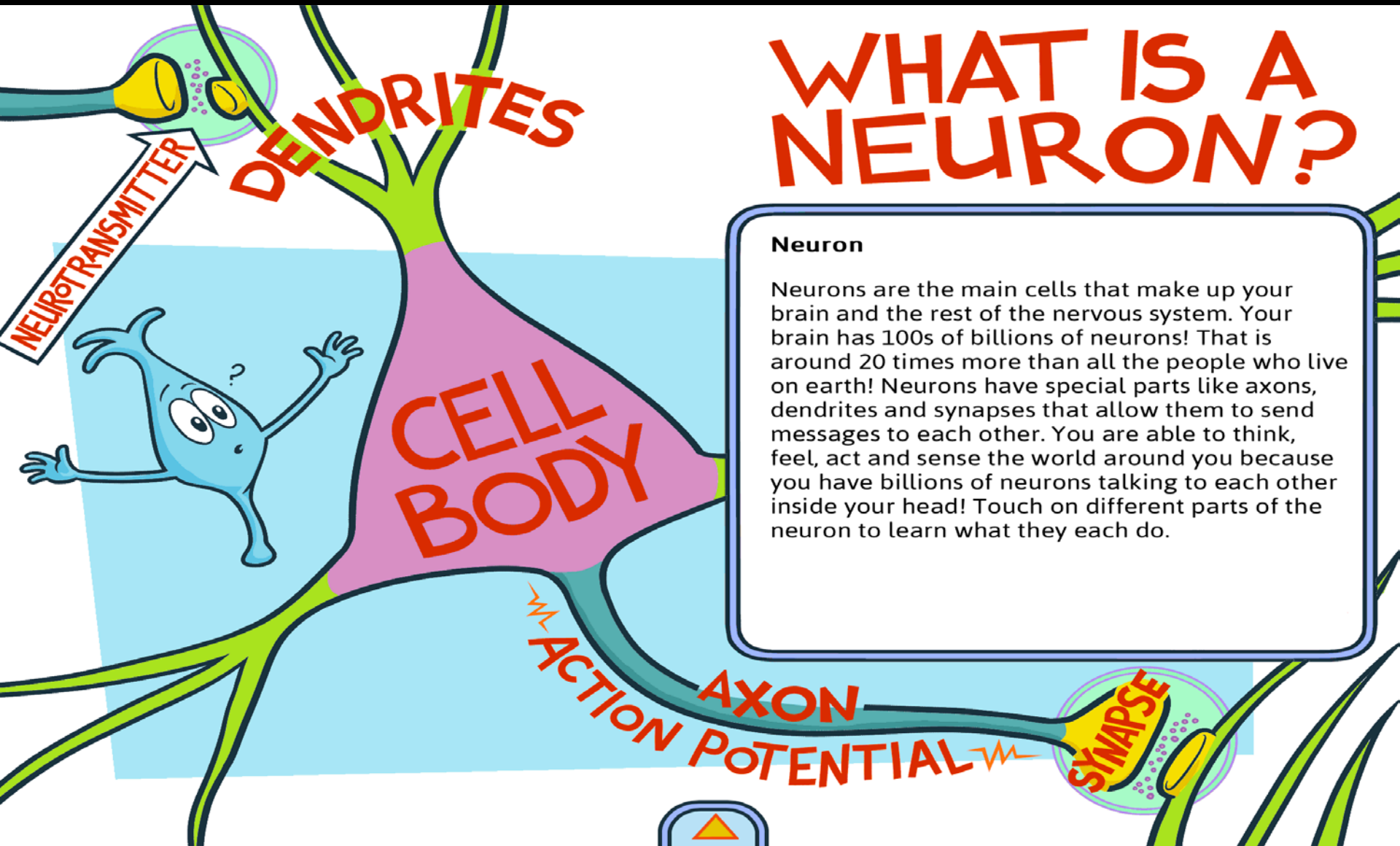
Gary Tsai, M.D.  
Medical Director  
Substance Abuse Prevention and Control

# Outline

- Neurobiology 101
- Neuroscience of Addiction & Recovery
- Medication-Assisted Treatment (MAT)
  - Myths: Fact and Fiction
  - FDA-approved medications & how they work
  - Evidence
- The Future
  - Implications
  - Innovations
  - Challenges

**\*Disclaimer:** Dr. Tsai has no relevant financial or non-financial relationships with the products or services described in this presentation.

# Neurobiology 101

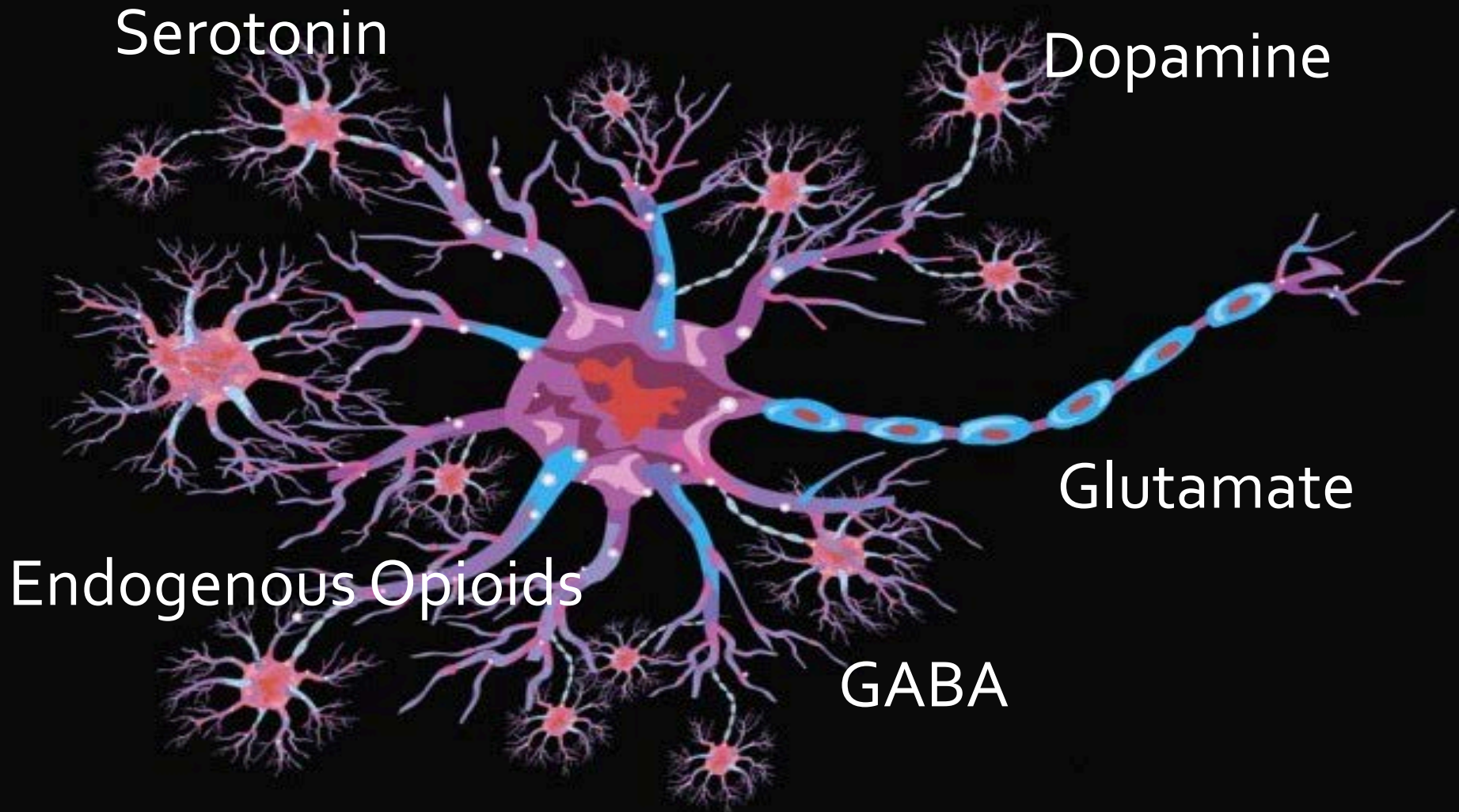


## WHAT IS A NEURON?

### Neuron

Neurons are the main cells that make up your brain and the rest of the nervous system. Your brain has 100s of billions of neurons! That is around 20 times more than all the people who live on earth! Neurons have special parts like axons, dendrites and synapses that allow them to send messages to each other. You are able to think, feel, act and sense the world around you because you have billions of neurons talking to each other inside your head! Touch on different parts of the neuron to learn what they each do.

# Neurobiology of Behavior: Neurons & Neurotransmitters



# The Brain: a Collection of Communicating Neurons

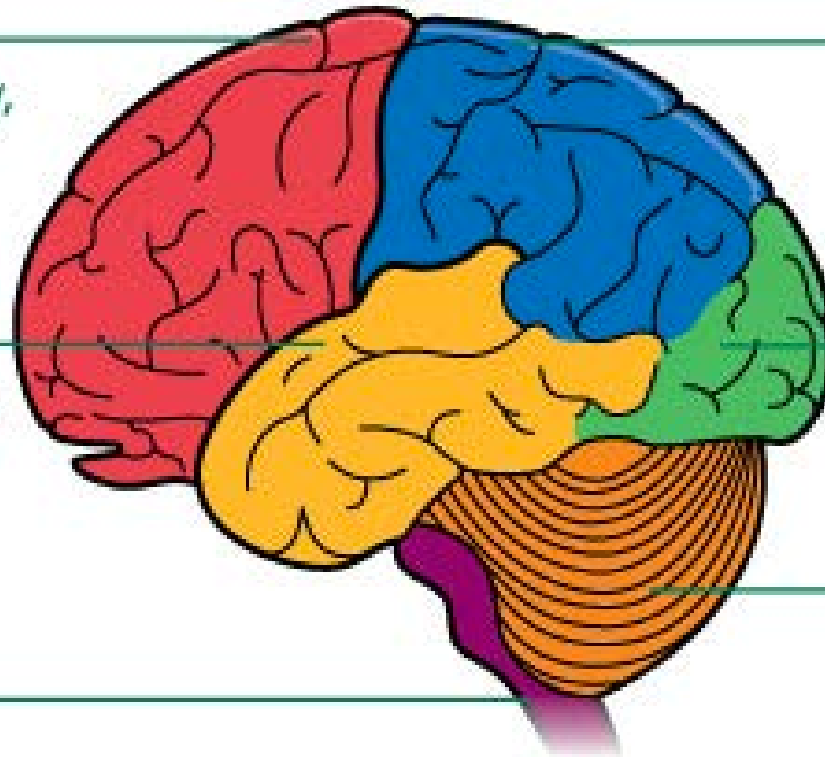


# Brain Regions

Frontal lobe  
(thinking, memory,  
behaviour and  
movement)

Temporal lobe  
(hearing, learning  
and feelings)

Brain stem  
(breathing,  
heart rate and  
temperature)



Parietal lobe  
(language  
and touch)

Occipital  
lobe (sight)

Cerebellum  
(balance and  
coordination)

# Neurobiology of Addiction

- Addiction is a brain disease

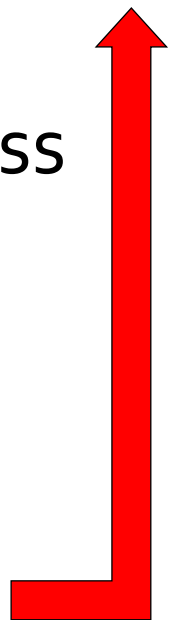
Repeated exposure to alcohol & other drugs (AOD)



Strengthening of memory connections across various brain circuits



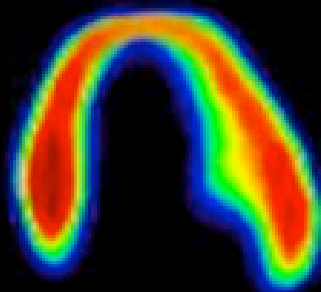
- Distortions in thinking
- Difficulty in dealing with emotions
- Compulsive use of AOD



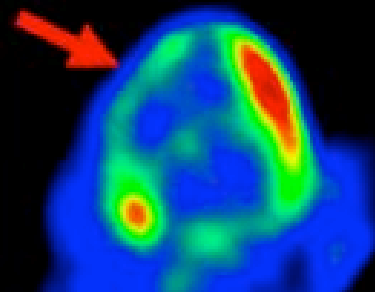
# ADDICTION IS A DISEASE OF THE BRAIN

*...as other diseases it affects the tissue function*

Decreased Heart Metabolism in Heart Disease Patient

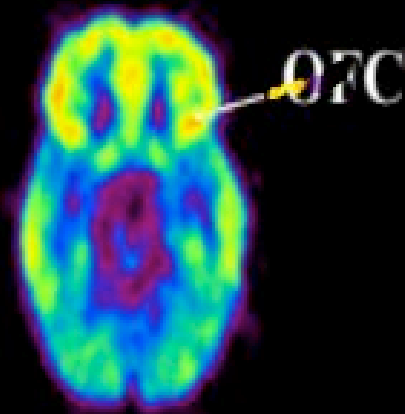


**No Heart Disease**

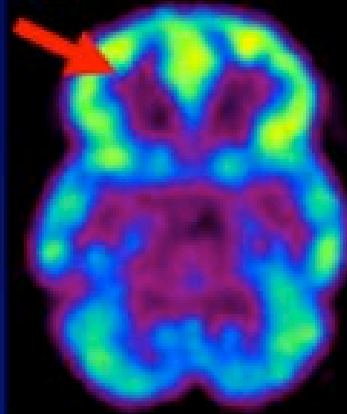


**Diseased Heart**

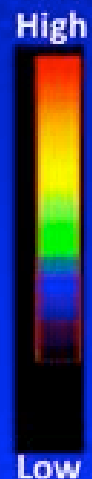
Decreased Brain Metabolism in Drug Abuse Patient



**No Cocaine Abuse**



**Cocaine Abuser**





# Comparing Relapse Rates Between Addiction and Other Chronic Conditions

## Percentage of Patients Who Relapse

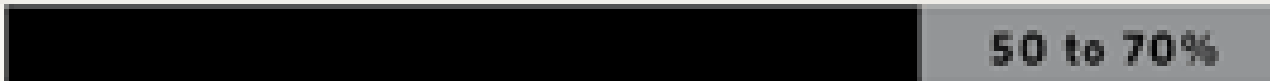
### TYPE I DIABETES



### DRUG ADDICTION



### HYPERTENSION

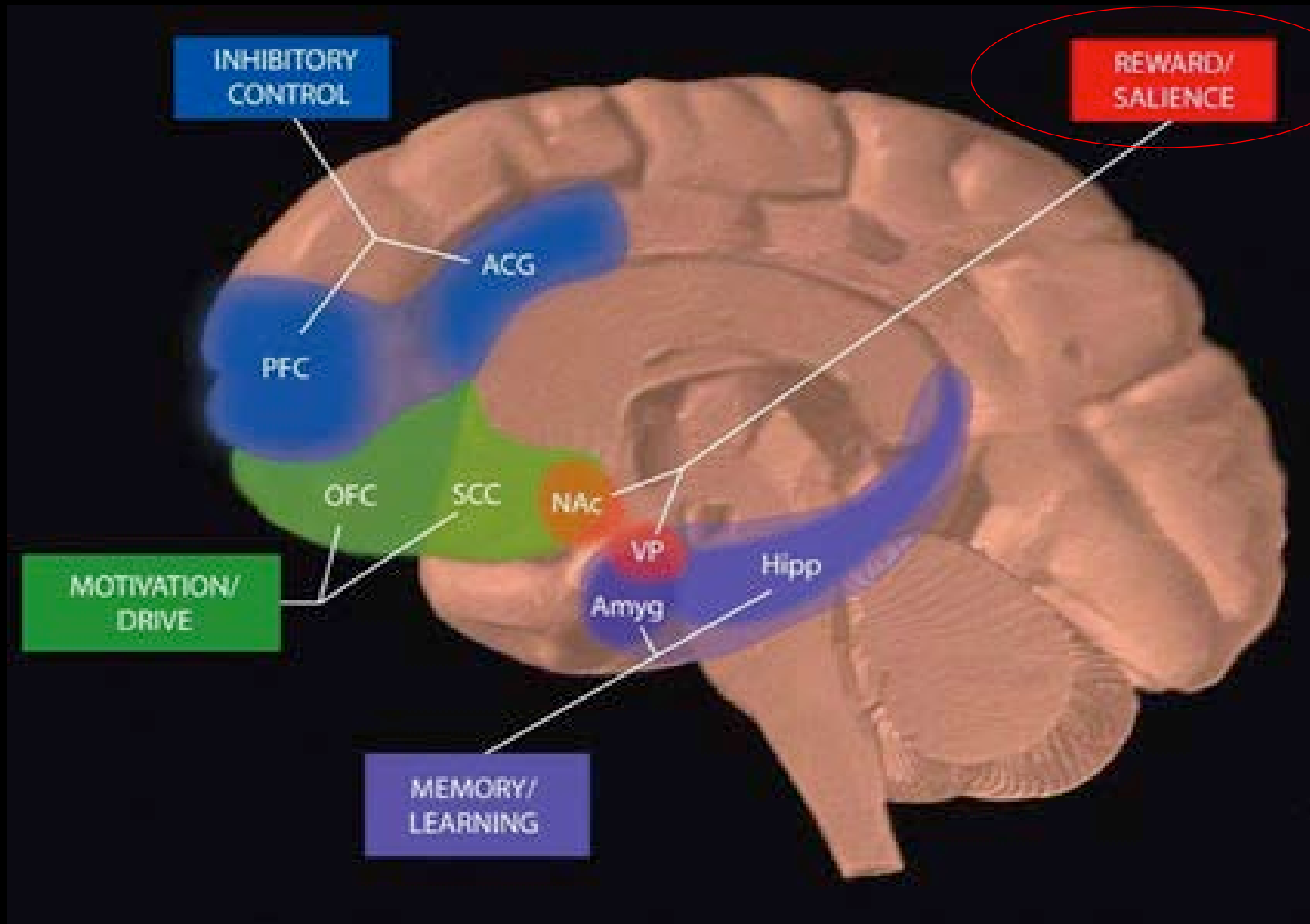


### ASTHMA



Source: McLellan, et al.,  
JAMA, 284: 1689 – 1695,  
2000 (via slides from NIDA).

# Brain Circuits Involved in Addiction



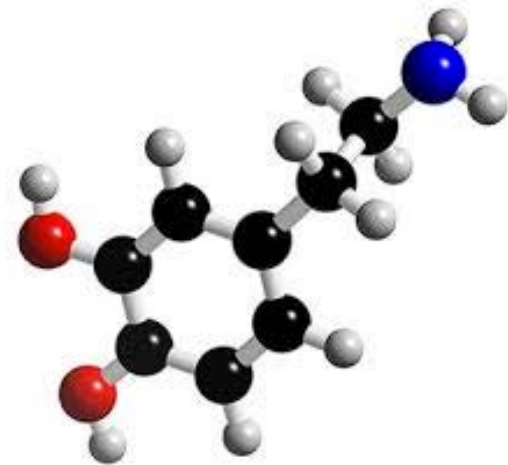
# The Reward Pathway

- Primary circuit involved in addiction
- Drugs and alcohol act on the same reward pathways as other pleasurable activities:
  - Eating
  - Sex
  - Exercise

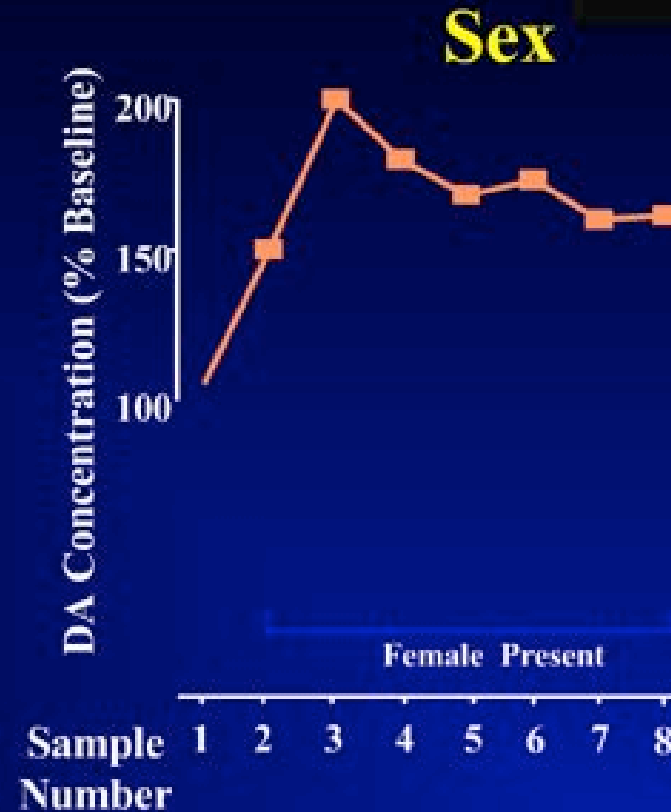
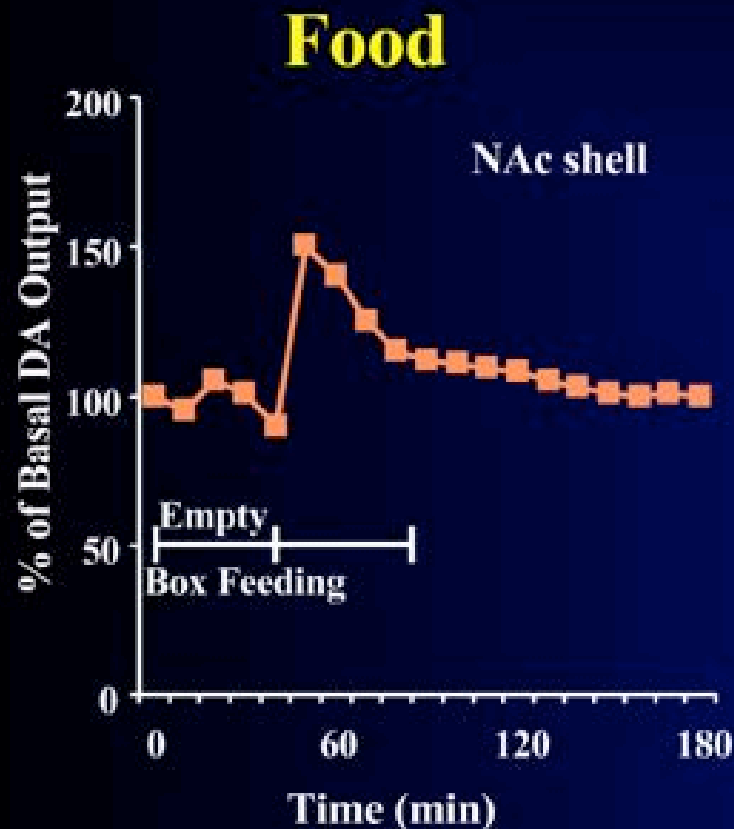
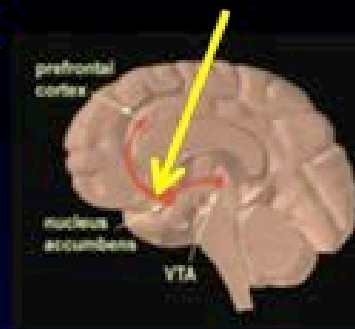


# Dopamine: the Pleasure Chemical

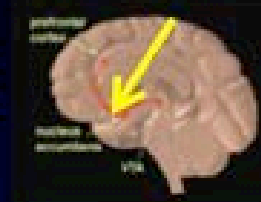
- Dopamine is the neurotransmitter that's most responsible for pleasure.
- Important for attention, problem solving, and anticipation of reward.
- Implicated in:
  - Drug "high"
  - Cravings



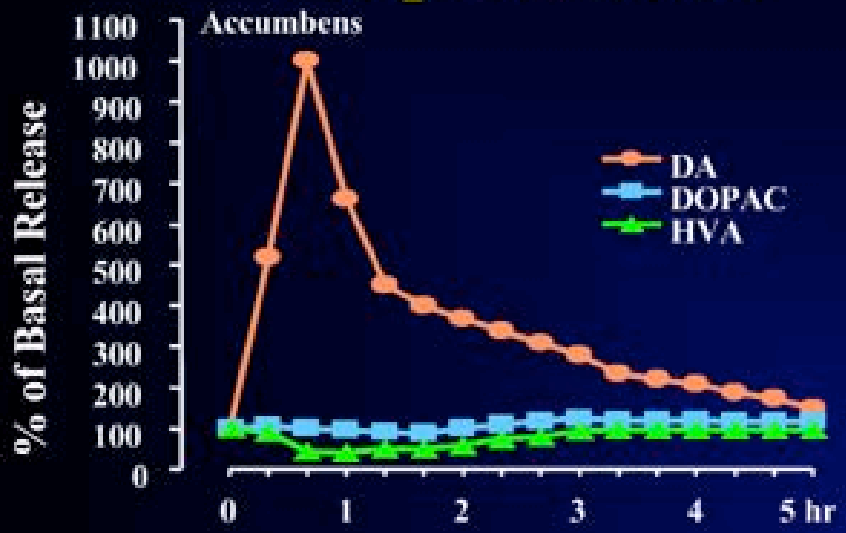
# Natural Rewards Elevate Dopamine Levels



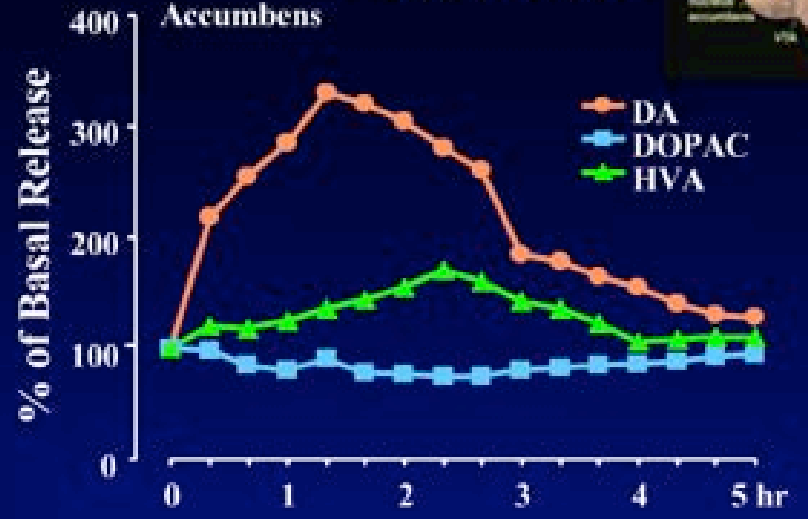
# Drugs Elevate on Dopamine Release



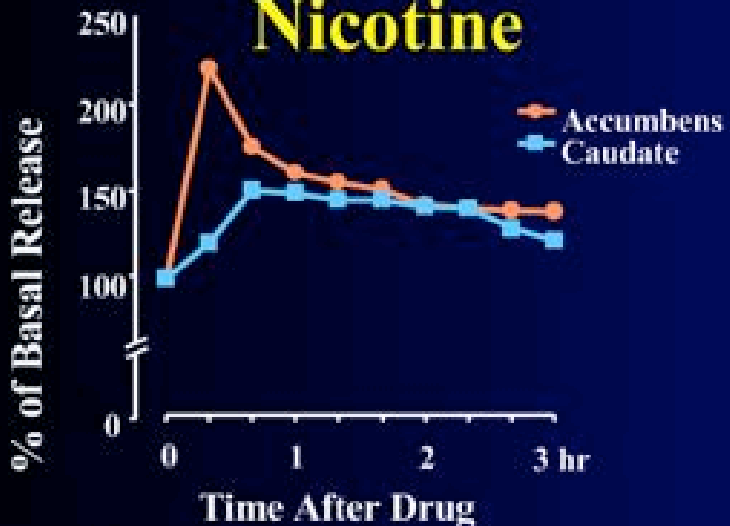
## Amphetamine



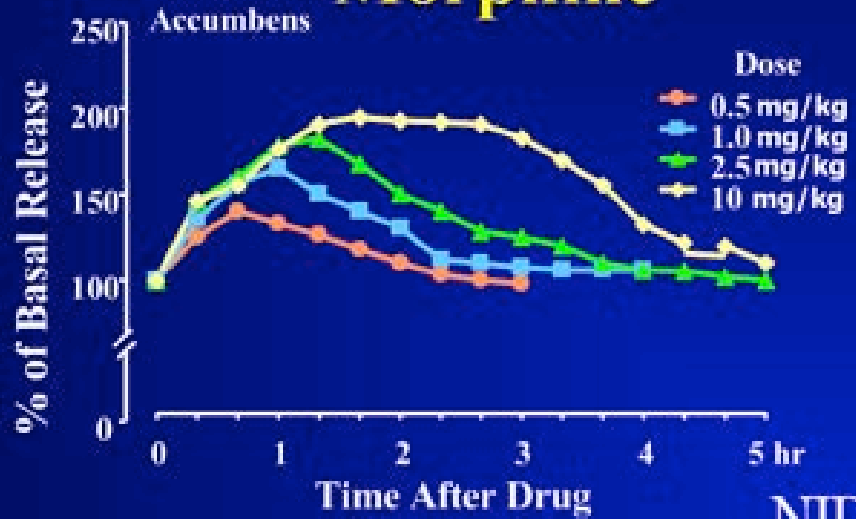
## Cocaine



## Nicotine



## Morphine

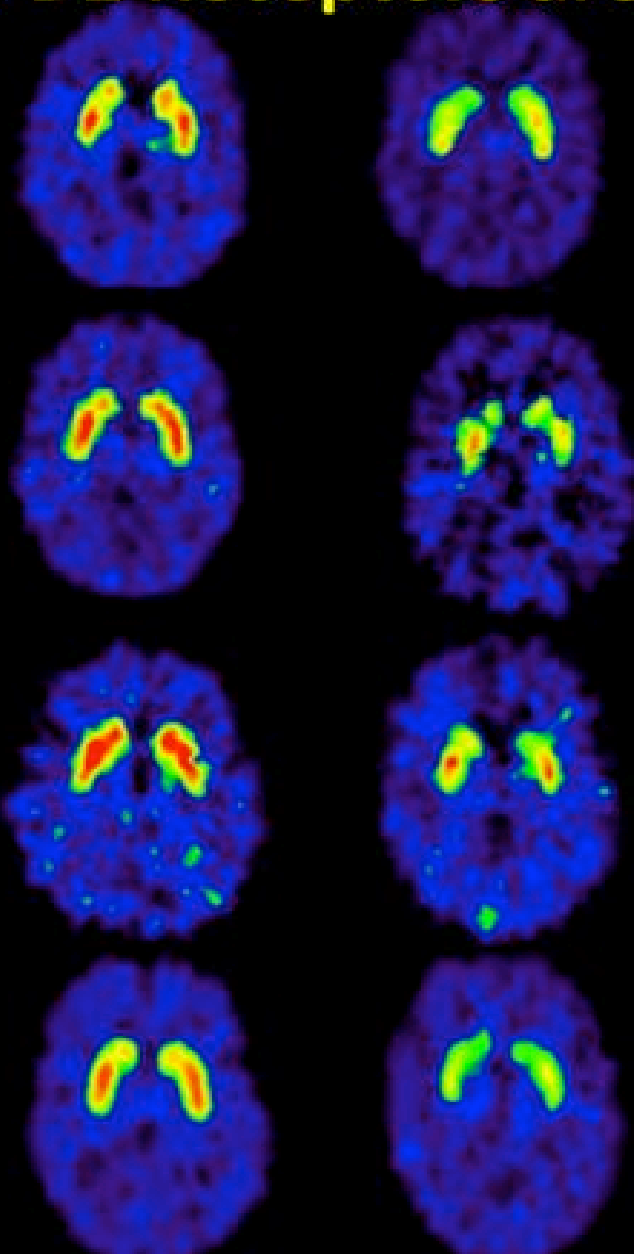


# Substances Affect the Brain in 3 Main Ways

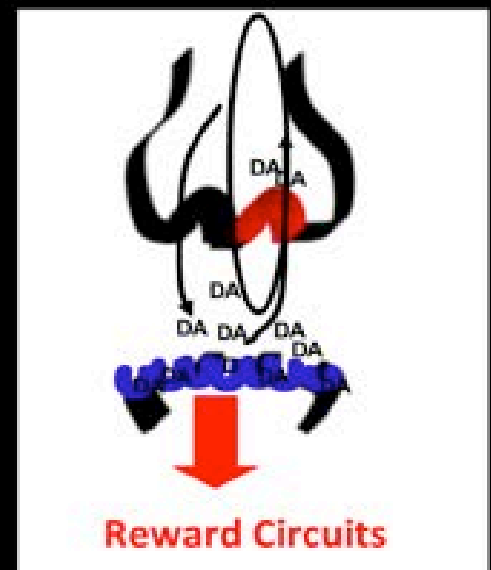
- Chemically
- Structurally
- Behaviorally



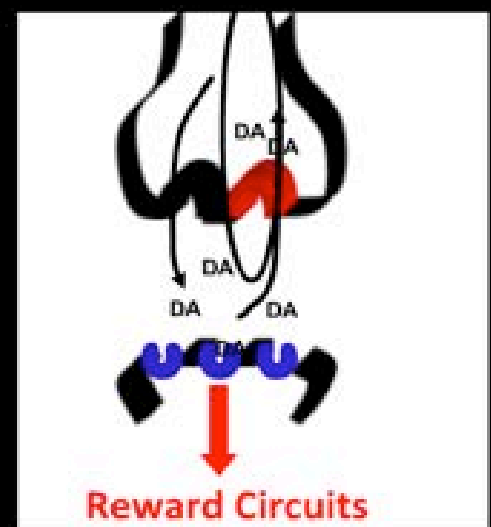
# Dopamine D2 Receptors are Lower in Addiction



DA D2 Receptor Availability



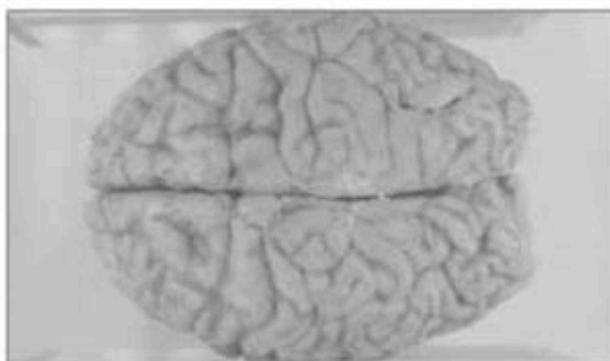
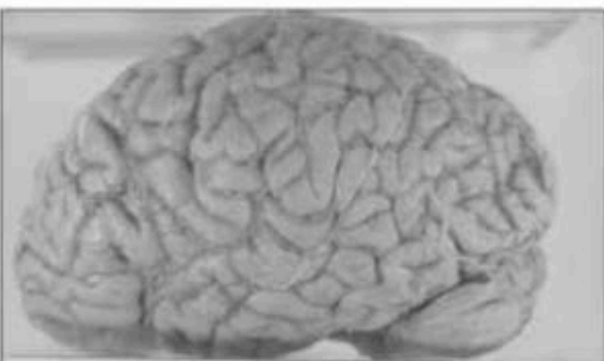
*Non-Drug Abuser*



*Drug Abuser*

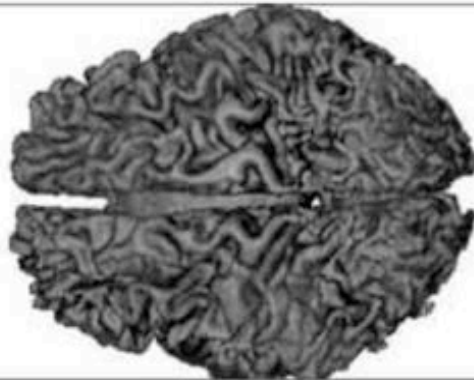
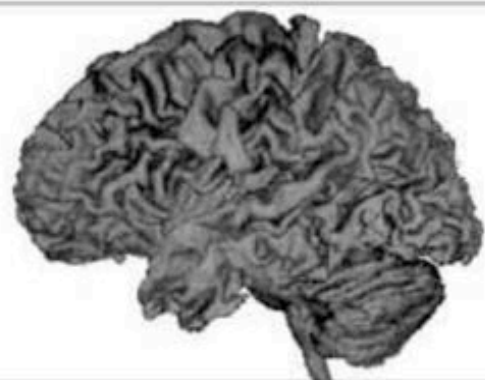
Source: NIDA





**healthy  
elderly  
person**

**person with  
Alzheimer's  
disease**

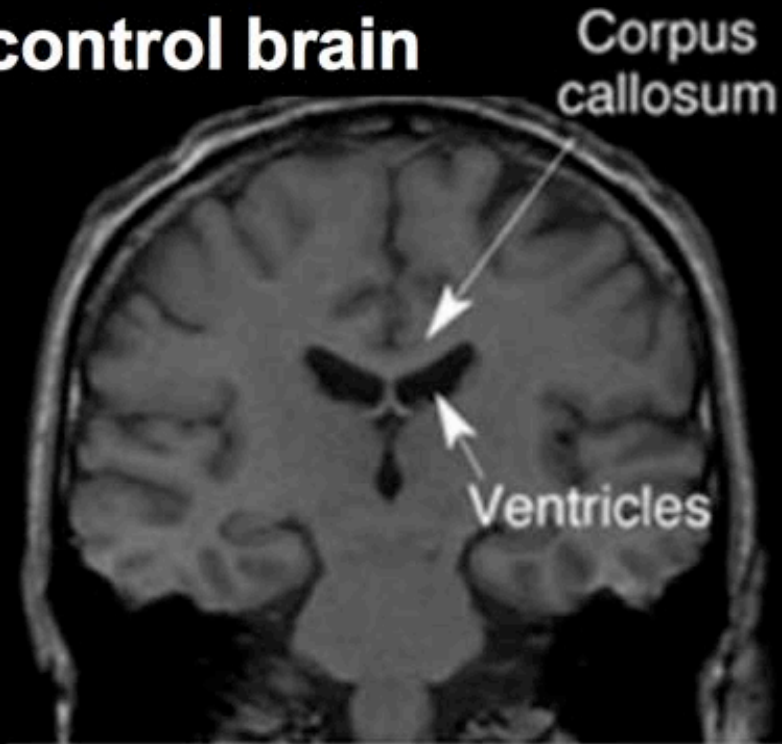


**heavy  
drinker**

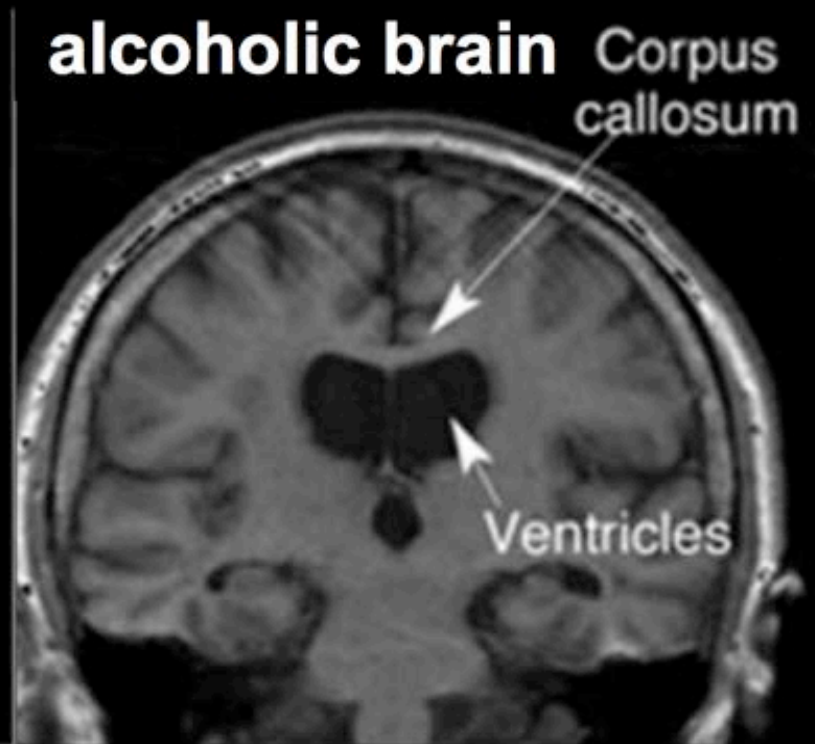
*(National Institute on Alcohol Abuse & Alcoholism, 2004)*

# Structural Changes from AOD Use

**control brain**



**alcoholic brain**



*(National Institute on Alcohol Abuse & Alcoholism, 2004)*

# Behavioral Changes from AOD Use

- Classical & Operant Conditioning
  - Behaviors that are REWARDED are likely to be REPEATED

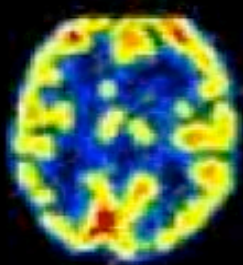
Positive reinforcement → drug high



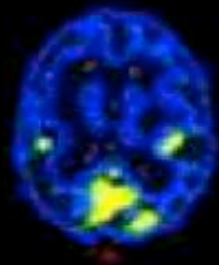
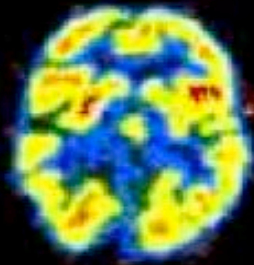
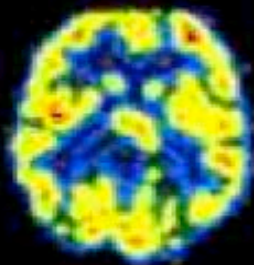
Negative reinforcement → drug relapse secondary to withdrawal symptoms



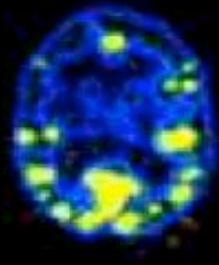
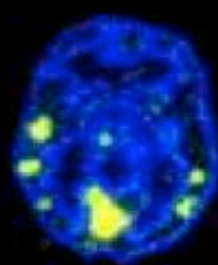
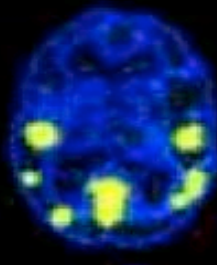
# Neurobiology of Recovery



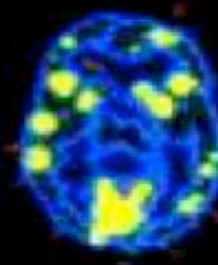
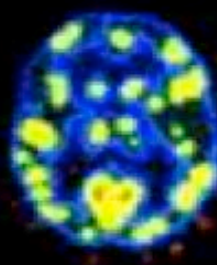
healthy brain



cocaine abuser (10 days clean)

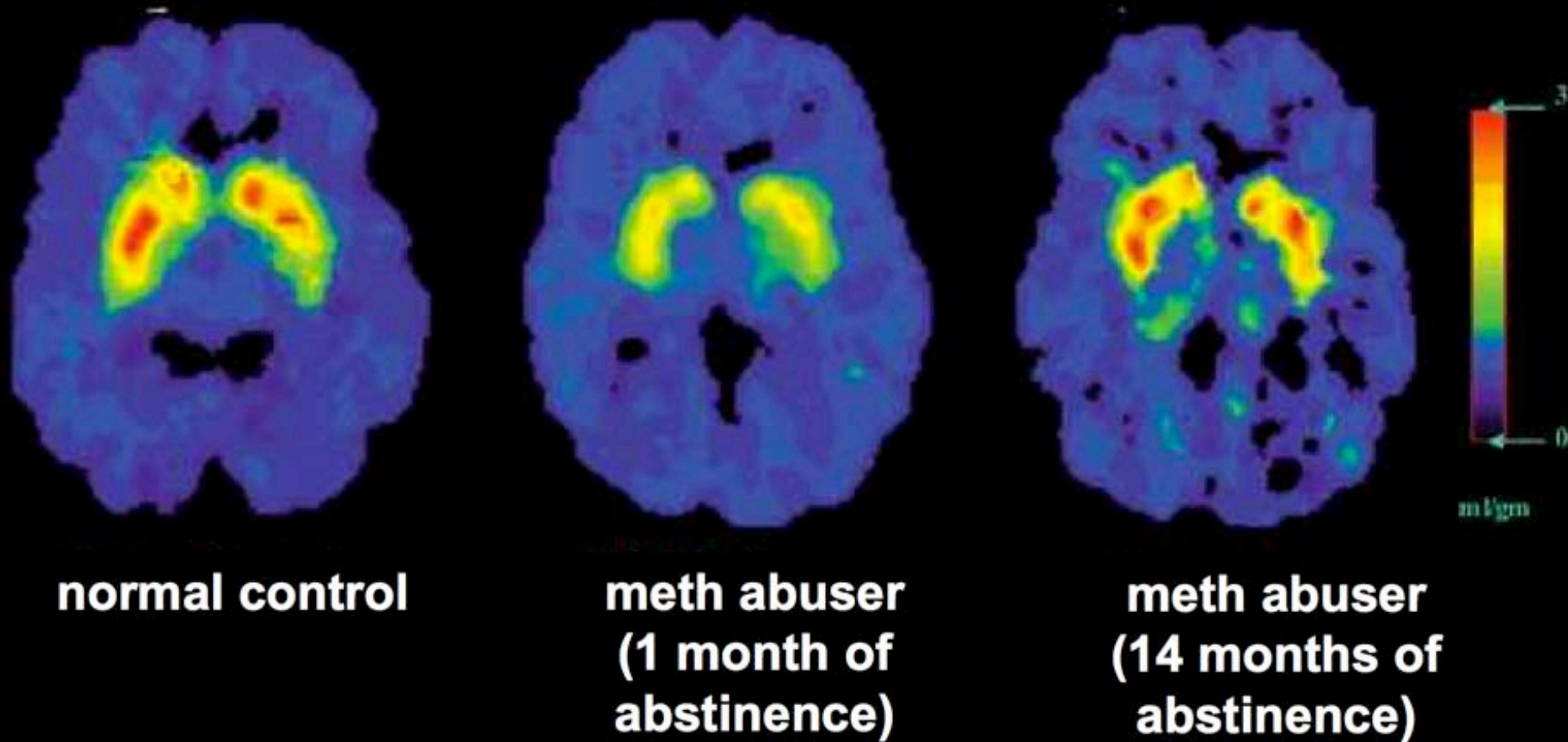


cocaine abuser (100 days clean)



level of brain activity  
(low to high)

# Neurobiology of Recovery (cont'd)



*(National Institute on Drug Abuse, 2002)*

# Medication-Assisted Treatments (MAT)

- MAT is the use of pharmacological interventions (aka: medications) in combination with counseling and behavioral therapies to provide a comprehensive and whole-person approach to SUD treatment.



# MAT's Role in SUD Treatment

- Complex problems generally require multifaceted solutions.
- Best practice for the treatment of most chronic conditions require both pharmacologic and lifestyle/behavioral interventions:
  - Diabetes, Hypertension, etc. → meds + lifestyle/behavioral counseling (diet, exercise, talk therapy, etc.)
  - Addiction → meds + counseling/therapy



# MAT's Role in SUD Treatment (cont'd)

- Research has shown that when treating SUDs, a combination of medication and behavioral therapies is more effective than either intervention alone.





# When to Start MAT

- Scientific evidence supports the fact that MAT improves success rates in the first 6 months of recovery.
- Individuals who remain sober during this critical period significantly improve their chances of sustained recovery.
- MAT definitively increases the % of people who remain abstinent during this important time.
- **MAT SHOULD BE STARTED EARLY IN TREATMENT!**

# Off-Label Prescribing

- **While all FDA-approved medications have been shown to be effective, not all effective medications have been FDA-approved.**
- Obtaining FDA-approval is a costly process and many factors other than effectiveness contribute to the decision about whether to seek FDA-approval.
- Some “off-label” medications have been effectively used in other countries for years or even decades, even if they are not FDA-approved in the U.S.
- Examples of medications that are sometimes used off-label for various SUDs:
  - Gabapentin
  - Topiramate
  - Clonidine
  - Carbamazepine

FACTS

~~MYTHS~~

# MAT: Fact and Fiction

- **Myth #1: I recovered from addiction without using MAT, therefore it's unnecessary.**
- While it's true that many people have achieved recovery without MAT, it's also true that many people have recovered from infections prior to the invention of antibiotics... this does not mean that we should not use antibiotics when appropriate.
- **FACT:**
  - Paths to recovery are not the same for everyone.
  - While personal experiences and beliefs are important, clients' recovery journeys don't necessarily need to parallel our own.
  - Treatments should change with science, technology, and evidence.
  - If scientific advances can make the recovery process easier and improve outcomes, clinicians have a responsibility to provide care that is in the best interests of their clients.

# MAT: Fact and Fiction (cont'd)

- Myth #2: MAT is just replacing one drug with another.
- FACT:
  - There are important differences between MAT and illicit drugs:

MAT	Illicit Drugs
Prescribed/monitored by a medical professional	Obtained illegally
FDA-approved	Not legally permitted
Regulated potency	Potency varies
Curbs cravings and withdrawal	Causes euphoria and a "high"
Generally: Risks < Benefits	Generally: Risks > Benefits

# MAT: Fact and Fiction (cont'd)

- Myth #3: MAT doesn't work.

- FACT:

- FDA-approval is granted only if effectiveness and safety have been proven.
- Assuming appropriate dosing, numerous studies have definitively demonstrated that MAT works.
- Demonstrated benefits of MAT:

INCREASE	DECREASE
Treatment retention	Cravings
Likelihood for abstinence	Drug-related deaths
Employment rates	Risk of relapse on alcohol
	Total # of drinking days
	Opioid use
	Criminal activities

# MAT: Fact and Fiction (cont'd)

- **Myth #4: If someone is clean from substances, they don't need MAT.**
- **FACT:**
  - If addiction were episodic, this would be true, similar to how antibiotics are not necessary after an infection has cleared.
  - **HOWEVER**, chronic conditions (i.e.: addiction) often require long-term treatment interventions.
    - For example, once someone's blood sugar or blood pressure is stabilized, they still need to continue taking their diabetes or blood pressure medications in order to maintain stability → The same is true for MAT and addiction!

# FDA-Approved MAT

- **Opioid use disorder**
  - Methadone
  - Buprenorphine
  - Naltrexone (oral & long-acting injectable)
    - \*Naloxone (used for overdose, not maintenance treatment)
- **Alcohol use disorder**
  - Naltrexone (oral & long-acting injectable)
  - Disulfiram
  - Acamprosate
- **Tobacco use disorder**
  - Bupropion
  - Varenicline



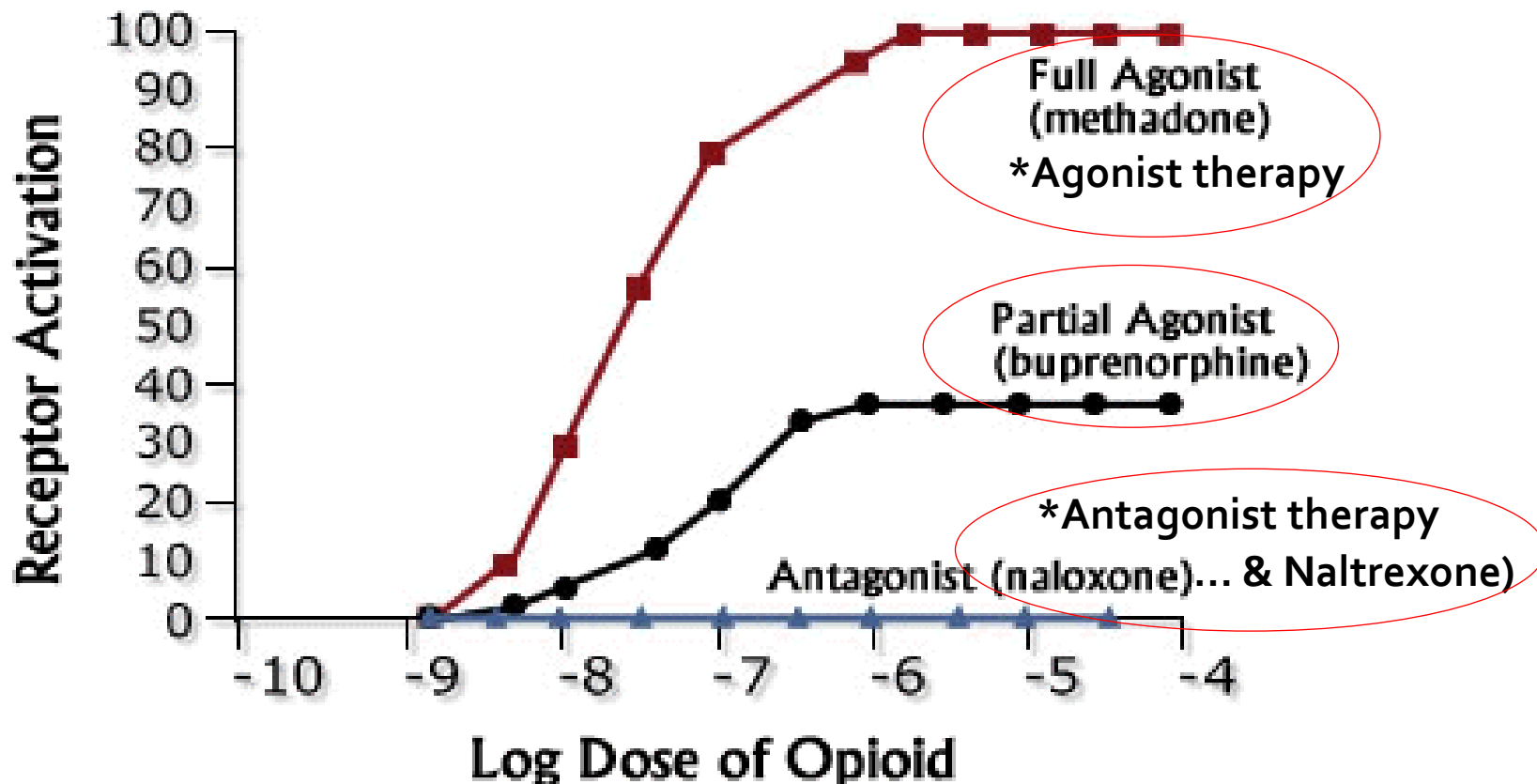
# MAT for Opioid Use Disorders



Poppy Plant

# How MAT for Opioid Use Disorder Works

## Receptor Activation: Full Agonist, Partial Agonist, Antagonist



# SYNAPSE



Heroin

Buprenorphine

Naltrexone

Methadone

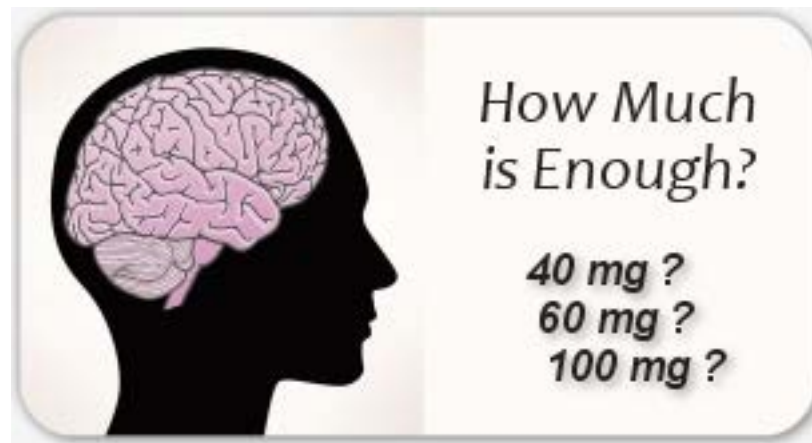
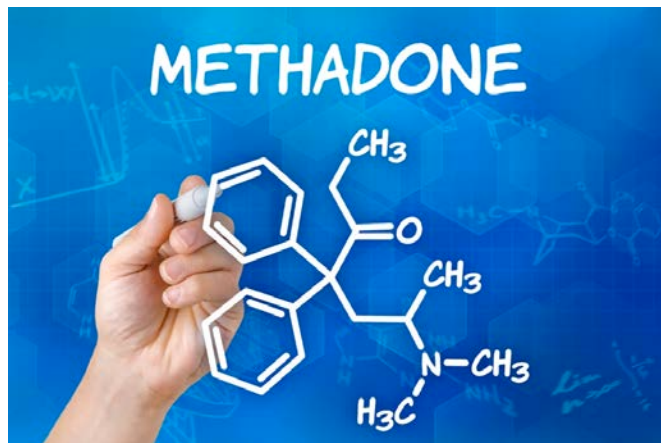
OPIOID  
RECEPTOR

Receptor  
Activity  
Varies



# Methadone

- Mechanism → Full agonist, acts on mu opioid receptor
- Long-acting (less habit-forming than shorter-acting agents, such as heroin)
- Alleviates withdrawal symptoms & cravings
- Typical therapeutic dose → 80 – 120 mg daily



# Methadone: Pros & Cons

- Pros:
  - Assuming appropriate oral dosing, very effective
  - Excellent option for those who haven't responded to other medications
  - Required structure of daily visits to OTPs- a pro for some and a con for others
  - Low cost
  - Demonstrated safety for pregnant women
- Cons:
  - Daily visits to OTPs
  - If dosed inappropriately too high, may cause euphoria or overdose

# Methadone: The Evidence

- In 204 prison inmates given methadone + counseling vs. counseling alone
  - Methadone group had 50% reduction in inmates who tested (+) for opioids after 1 year.
  - Treatment retention after 1 year:
    - 33% of the methadone + counseling group still in treatment.
    - 0 clients from the counseling only group still in treatment.

# Buprenorphine

- Mechanism → Partial mu receptor agonist, with “ceiling” effect
- Long-acting
- Blocks euphoric effect of opioids, alleviates withdrawal and cravings
- Schedule III → Office-based
- Suboxone = Buprenorphine + Naloxone
  - Naloxone in Suboxone discourages diversion and abuse
- Must dose when client is abstinent or in slight withdrawal
- Typical therapeutic dose → 8 mg /2 mg – 16 mg /4 mg daily
  - Oral or sublingual formulation



# Buprenorphine: Pros & Cons

## ■ Pros:

- More convenient, office-based dosing, compared to Methadone
- Less risk of euphoria and OD
- Easier to taper than Methadone, when that is the goal
- Growing evidence supporting safety for pregnant women (NOT Naloxone) and decreased rates of Neonatal Abstinence Syndrome compared to Methadone

## ■ Cons:

- High cost
- Prescriber must have special training/certification to prescribe Buprenorphine
- Diversion- some people do better with the structured Methadone regimen (required to go into an OTP regularly for dosing)



# Buprenorphine: The Evidence

- Cochrane systematic review and meta-analysis of 24 randomized controlled trials comparing maintenance treatment with Buprenorphine vs. Methadone vs Placebo (4500 patients)
  - Buprenorphine group was significantly superior to placebo in treatment retention and suppressing heroin use
  - Comparing Buprenorphine vs. Methadone
    - For those who remained in treatment → Buprenorphine ≈ Methadone
    - Dose dependent findings (medium Buprenorphine dose > low Methadone dose at heroin suppression, etc)
    - If relative doses are equal → Methadone > Buprenorphine
- However, when deciding treatments, there is MUCH more that needs to be factored in than simply which medication is more effective at a given dose (i.e.: safety, client preference, risk of diversion, severity of dependence, etc.)

# Naltrexone

- Mechanism → Full antagonist of various opioid receptors
- Blocks euphoric effects of opioids and decreases risk of impulsive use of opioids
- Oral and long-acting injectable formulation (Vivitrol) available
- Typical therapeutic doses:
  - Oral formulation: 50 mg qd, 100 mg q2days, 150 mg q3day
  - Injectable formulation: 380 mg IM qmonthly



# Naltrexone for Opioid Use: Pros & Cons

- Pros:
  - Non-addictive, blocks “high”
  - Convenient, office-based dosing
  - Monthly Vivitrol dosing eliminates need for daily dosing
- Cons:
  - Non-compliance with oral formulation
  - Requires prolonged abstinence (e.g.: 7 days) before initiation of Naltrexone
  - Cost (for Vivitrol)

# Naltrexone for Opioid Use: The Evidence

- Cochrane systematic review involving 13 randomized controlled trials and 1158 participants
  - Naltrexone vs Placebo vs Psychotherapy alone
  - If adherence is enforced, Naltrexone showed statistically significant ↑ in treatment retention and abstinence
  - HOWEVER, without enforced adherence, Naltrexone did not perform better than placebo or psychotherapy alone
  - When comparing Naltrexone vs. Buprenorphine, Buprenorphine outperformed Naltrexone
- Conclusion → Naltrexone works, but only when patients are adherent to the medication; poor treatment adherence to oral Naltrexone
  - Vivitrol → improved adherence

# MAT for Opioid Use Disorder During Pregnancy

- Benefits of treatment of mother with MAT during pregnancy **greatly outweigh** the risks of not addressing opioid use
- Methadone vs. Buprenorphine
  - **Methadone** is most well studied MAT for opioid addiction during pregnancy and has demonstrated safety during pregnancy for mother and fetus
    - Neonatal Abstinence Syndrome → infant experiences opioid withdrawal at birth
  - **Buprenorphine** is newer, but data is accumulating that Buprenorphine is a safe alternative to Methadone, with LESS RISK of Neonatal Abstinence Syndrome for the infant



**↑ Treatment Retention**

**↓ Overdose Risk**

**Demonstrated Benefits  
of MAT for Opioid Use  
Disorders**

**↓ Opioid Use**

**↑ Employment**

**↓ Criminal Activity**

**↑ Functioning**



# **MAT for Alcohol Use Disorders**

# Naltrexone

- Mechanism → Full antagonist of various opioid receptors
  - Since endogenous opioids are involved in reinforcing effects of alcohol, blocking these receptors results in decreased cravings and relapse
- Oral and long-acting injectable formulation (Vivitrol) available
  - Vivitrol results in more stable blood levels of Naltrexone compared to oral formulation
- Typical therapeutic doses:
  - Oral formulation: 50 mg qd
  - Injectable formulation: 380 mg IM qmonthly



\*See Naltrexone details from prior slide for opioid use disorder



# Naltrexone for Alcohol Use: The Evidence

- Cochrane systematic review involving 50 randomized controlled trials and 8000 participants
  - Naltrexone vs Placebo
    - ↓ in heavy drinking by 83%
    - ↓ in drinking days
    - ↓ in amount of alcohol consumption

# Vivitrol: Long-Acting Naltrexone

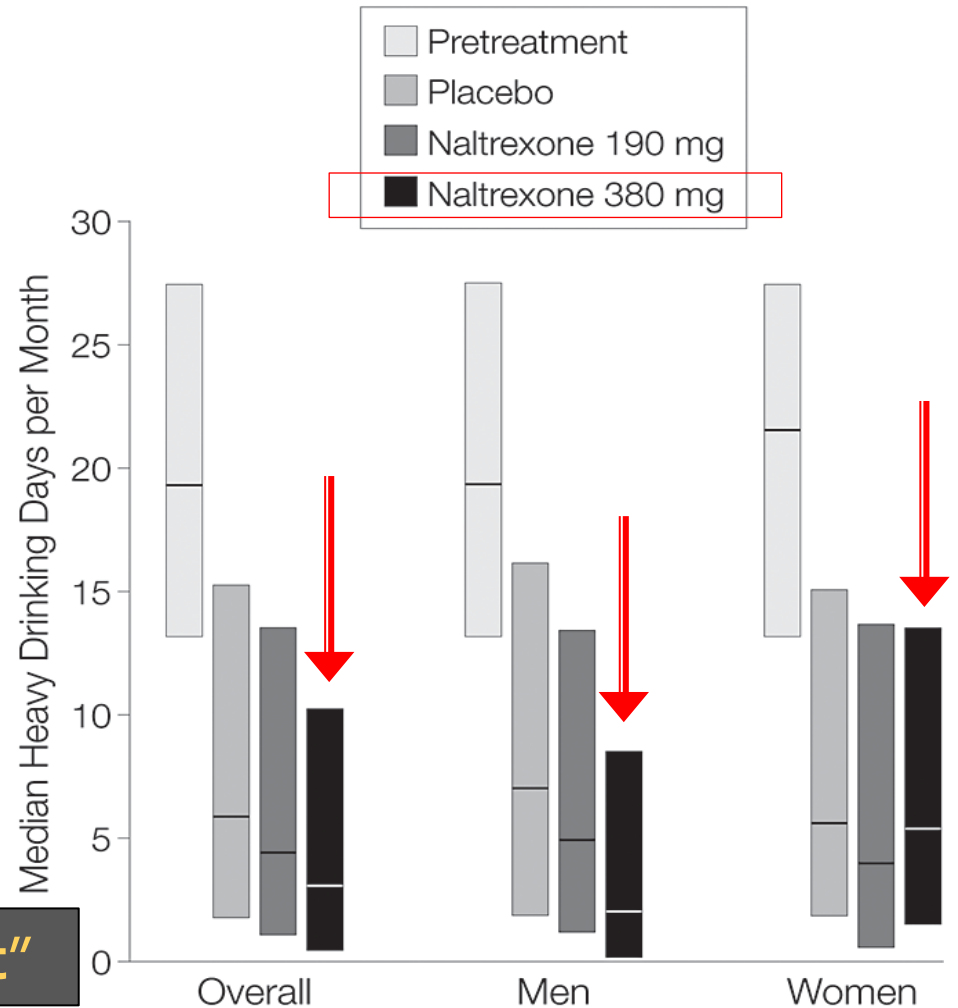
- Vivitrol = Naltrexone, just a different way of delivering the medication
- Less variability in medication levels in the blood  
→ less side effects for some
- Enhanced compliance compared to oral Naltrexone → clinically, this tends to result in improved outcomes
- Numerous studies have demonstrated similar outcomes with long-acting & oral formulation of Naltrexone<sup>1,2</sup>

1) Garbutt, J.C., et al. Efficacy and Tolerability of Long-Acting Injectable Naltrexone for Alcohol Dependence: A Randomized Controlled Trial. JAMA 2005; 293 (13): 1617-1625.

2) Krupitsky, E., et al. Injectable Extended-Release Naltrexone for Opioid Dependence : A Double-Blind, Placebo-CONtrolled, Multicentre Randomized Trial. Lancet 2011; 377(9776): 1506-1513.

# Vivitrol vs. Placebo

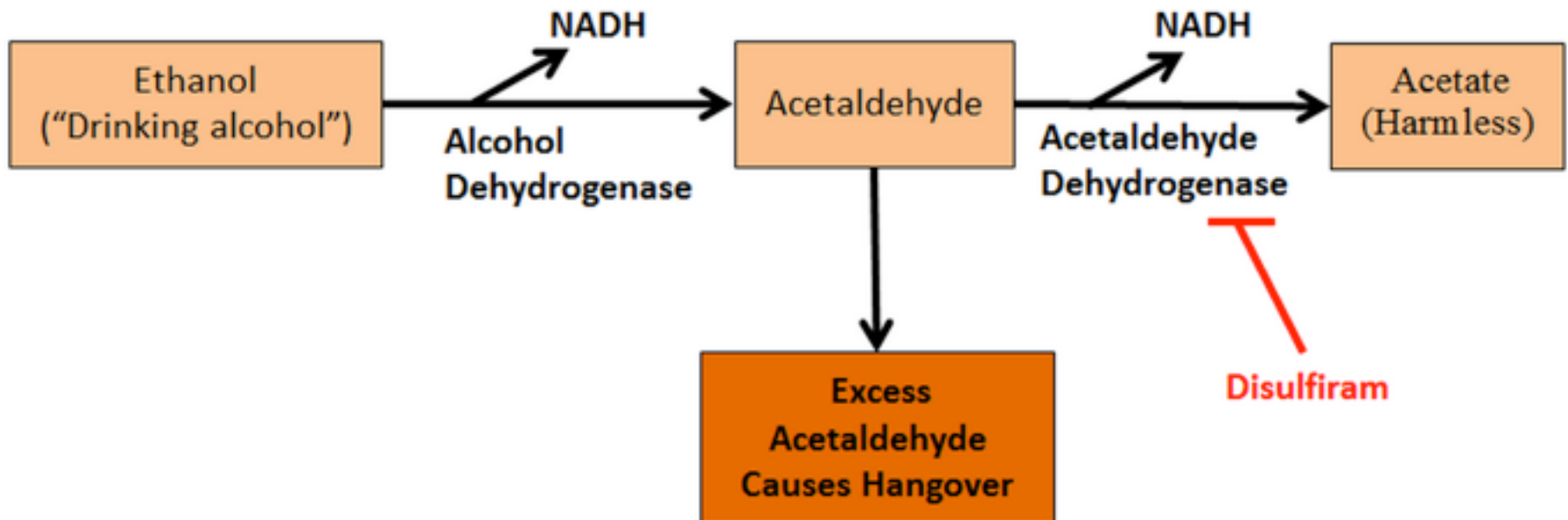
- Randomized, double-blind, placebo-controlled
- 6 month trial of 624 participants.
- 3 treatment groups
  - Placebo
  - Long-acting Naltrexone 190 mg
  - Long-acting Naltrexone 380 mg
- Result → ↓ heavy drinking days



**\*\*Interesting → "Placebo effect"**

# Disulfiram (Antabuse)

- Mechanism → Blocks acetaldehyde dehydrogenase, causing an excess build up of acetaldehyde



# Disulfiram (cont'd)

- “Aversion therapy” → Causes unpleasant physical effects after drinking (flushing, nausea, vomiting, etc.)
- Does not address cravings → poor compliance
- Typical therapeutic dose → 125-500 mg daily
  - Must be abstinent from alcohol for > 12 hrs before dose
- Pros:
  - Non-addictive
  - Low cost
  - Useful for motivated, chronic alcoholism
- Cons:
  - Poor compliance
  - Must be abstinent to initiate treatment
  - Avoid in severe heart disease or mental illness, particularly psychosis



# Disulfiram: The Evidence

- Meta-analysis including 22 studies
  - Disulfiram was effective when compared with controls, but only in open-label studies and not blind studies<sup>1</sup>
- Systematic review of 11 randomized controlled trials with 1530 participants<sup>2</sup>
  - Disulfiram had some effect on short-term abstinence, days until relapse, and # of drinking days
  - Long-term effects are unclear
- Overall, Disulfiram can be a useful tool, but not for everyone

1) Skinner, M.D., Lahmek, P., Pham, H., Aubin, H.J. (2014). Disulfiram Efficacy in the Treatment of Alcohol Dependence: A Meta-Analysis. PLoS ONE 9(2): e87366.

2) Jorgensen, C.H., Pedersen, B., & Tonnesen, H (2011). The Efficacy of Disulfiram for the Treatment of Alcohol Use Disorder. Alcoholism: Clinical and Experimental Research, 35: 1749-1758.

# Acamprosate

- Mechanism → Stabilizes glutaminergic hyperactivity during alcohol withdrawal
- Minimizes protracted alcohol withdrawal symptoms
- Typical therapeutic dose → 333-666 mg three times daily
- Pros:
  - Non-addictive
  - Low cost
- Cons:
  - Must be abstinent to initiate treatment



# Acamprosate: The Evidence

- Cochrane systematic review of 24 randomized controlled trials, including 6915 participants<sup>1</sup>
  - Compared to placebo, Acamprosate:
    - ↑ cumulative abstinence duration
    - ↓ risk of any drinking
- Meta-analysis of 19 published and 1 unpublished randomized control trial<sup>2</sup>
  - Compared to placebo, Acamprosate group had ↑ in continuous abstinence rate and treatment retention
- COMBINE study → Acamprosate no more effective than placebo.

1) Rosner, S., Hackl-Herrwerth, A., Leucht, S., Lehert, P., Vecchi, S., Soyka, M. Acamprosate for Alcohol Dependence. Cochrane Database of Systematic Reviews, 2010, Issue 9.

2) Mann, K., Lehert, P., Morgan, M.Y. (2004). The Efficacy of Acamprosate in the Maintenance of Abstinence in Alcohol-Dependent Individuals: Results of a Meta-Analysis. Alcoholism: Clinical and Experimental Research, 28(1): 51-63.

3) Anton, R.F., et al. (2006). Combined Pharmacotherapies and Behavioral Interventions for Alcohol Dependence: The COMBINE Study: A Randomized Controlled Trial. JAMA, 295(17): 2003-2017.



**↓ Relapses**

**↓ Alcohol consumption**

**Demonstrated Benefits  
of MAT for Alcohol Use  
Disorders**

**↑ Functioning**

**↑ Abstinence**

**↓ Total drinking days**

# MAT: Future Implications

- MAT provides another avenue to address addictions and synergize interventions (bio + psychosocial interventions).
  - Opportunity for integration with medical providers.
- Similar to the early days of psychiatric medications, the use of addiction medications will likely expand and eventually become mainstream.
  - Abstinence being defined as abstinence from both drugs and FDA-approved medications (as opposed to abstinence only applying to drugs) → contrary to the direction science is steering the field.
- The multifaceted nature of SUDs necessitates a continual balance between medical and psychosocial interventions.

# MAT: Future Innovations

- Buprenorphine
  - Injectable formulation → monthly
  - Implantable formulation → every 6 months
- NIDA is studying MAT that targets the kappa opioid receptor, as well as other novel medications for addiction
- “Precision medicine” → In the future, genetics may inform choice of MAT to individualize optimal SUD treatment.

# MAT: Barriers & Challenges

- Paucity of trained prescribers
- Negative attitudes and misinformation
- Policy and regulatory barriers
  - Financial coverage of MAT on formularies
  - Utilization management techniques such as annual or lifetime limits, “fail first” criteria, requiring initial authorization or reauthorization, etc.
  - Limitations on Buprenorphine prescribers

# Summary

- Addiction is a chronic condition with biopsychosocial origins → requires a multifaceted approach.
- Integrated care is important not just across systems of care (physical & mental health), but also within our own system of SUD care in terms of integrating various approaches into SUD services.
  - Medical model ~~OR~~ AND Social model
- MAT has demonstrated benefits that synergize with psychosocial interventions and is an important tool in the recovery toolbox, particularly EARLY IN TREATMENT

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CHANGE BRINGS  
**OPPORTUNITY.**  
-NIDO QUBEIN

**Thank you!**

