The background of the slide is a light gray gradient with several realistic water droplets of various sizes scattered across it. The droplets have highlights and shadows, giving them a three-dimensional appearance. The main title is centered in a large, bold, black sans-serif font.

# UNDERSTANDING ADDICTION

HOW SCIENCE INFORMS TREATMENT AND PREVENTION IN MODERN ADDICTION  
MEDICINE.

WARREN SEEDS, M.D., DABAM  
DIRECTOR OF ADDICTION MEDICINE,  
MONOS HEALTH, LAS VEGAS, NEVADA



THERE ARE NOW  
**MORE DEATHS FROM  
OVERDOSE**

THAN AUTOMOBILE ACCIDENTS.

IN 2014, OVER **29,467** PEOPLE IN THE US DIED FROM OPIOID OVERDOSE. END-TO END, THEIR CASKETS  
WOULD FORM A LINE 37 MILES LONG.



# 4 IN 5 HEROIN USERS

- STARTED WITH PRESCRIPTION OPIOIDS.

# IN 2010

- 4.6% OF THE WORLD'S POPULATION LIVED IN THE U.S.
- 80% OF THE WORLD'S OPIOIDS WERE CONSUMED IN THE U.S.
- 99% OF THE WORLD'S HYDROCODONE WAS CONSUMED IN THE U.S.



- THAT'S 5MG OF HYDROCODONE EVERY 4 HOURS...

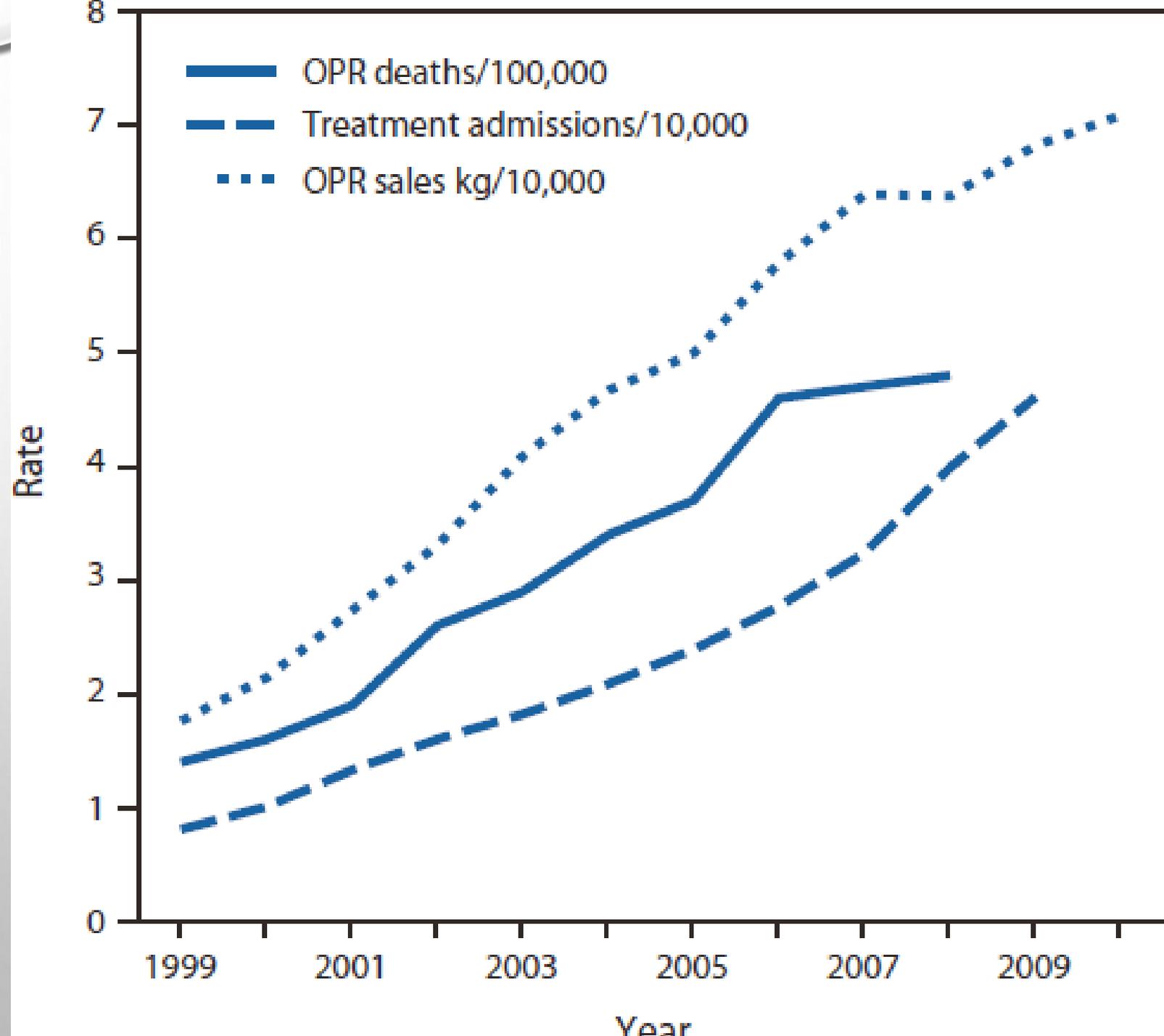
- FOR **EVERY MAN, WOMAN AND CHILD IN  
THE U.S. ...**

- FOR **30 DAYS**

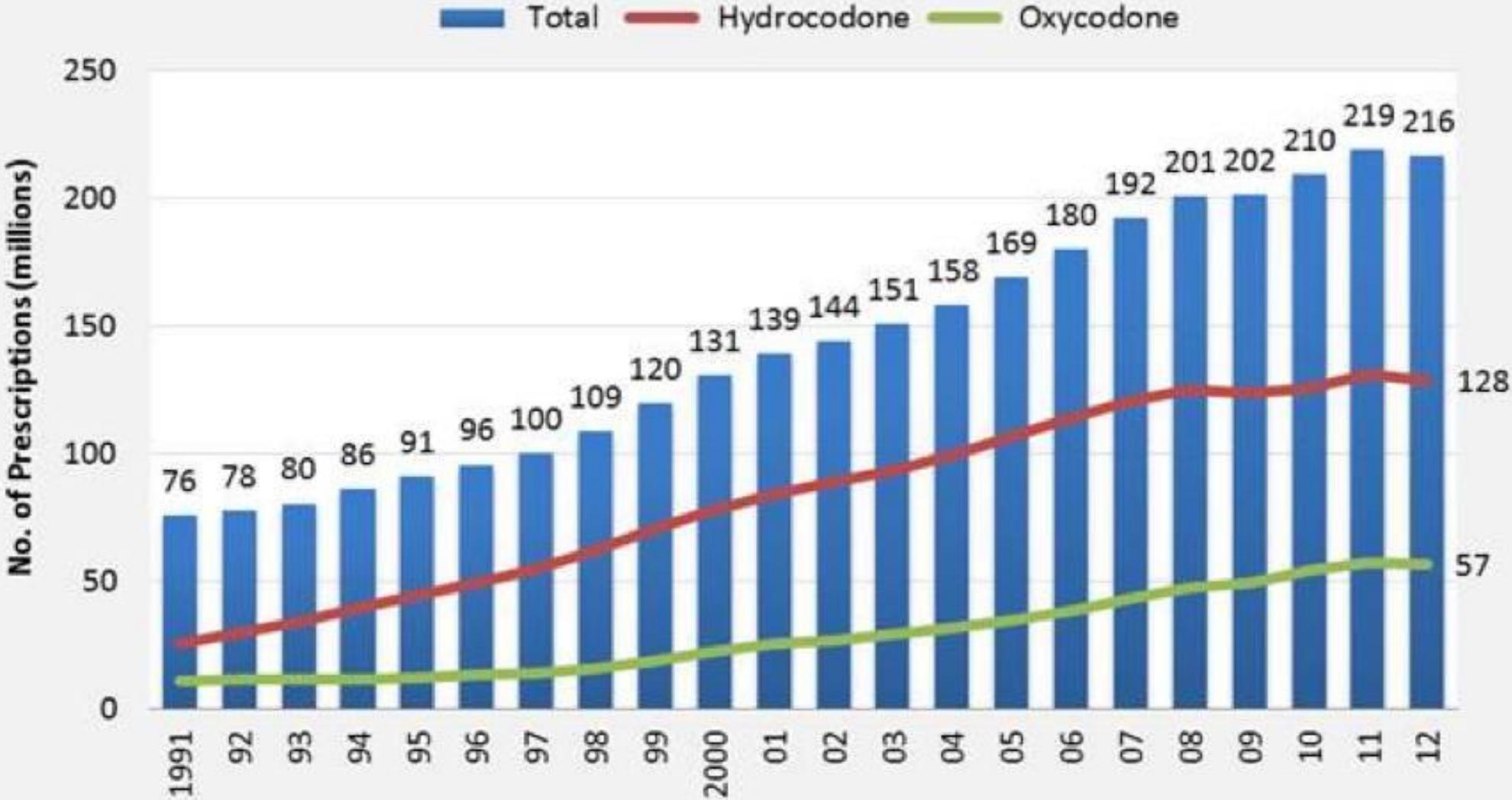


# HOW DID WE GET HERE?

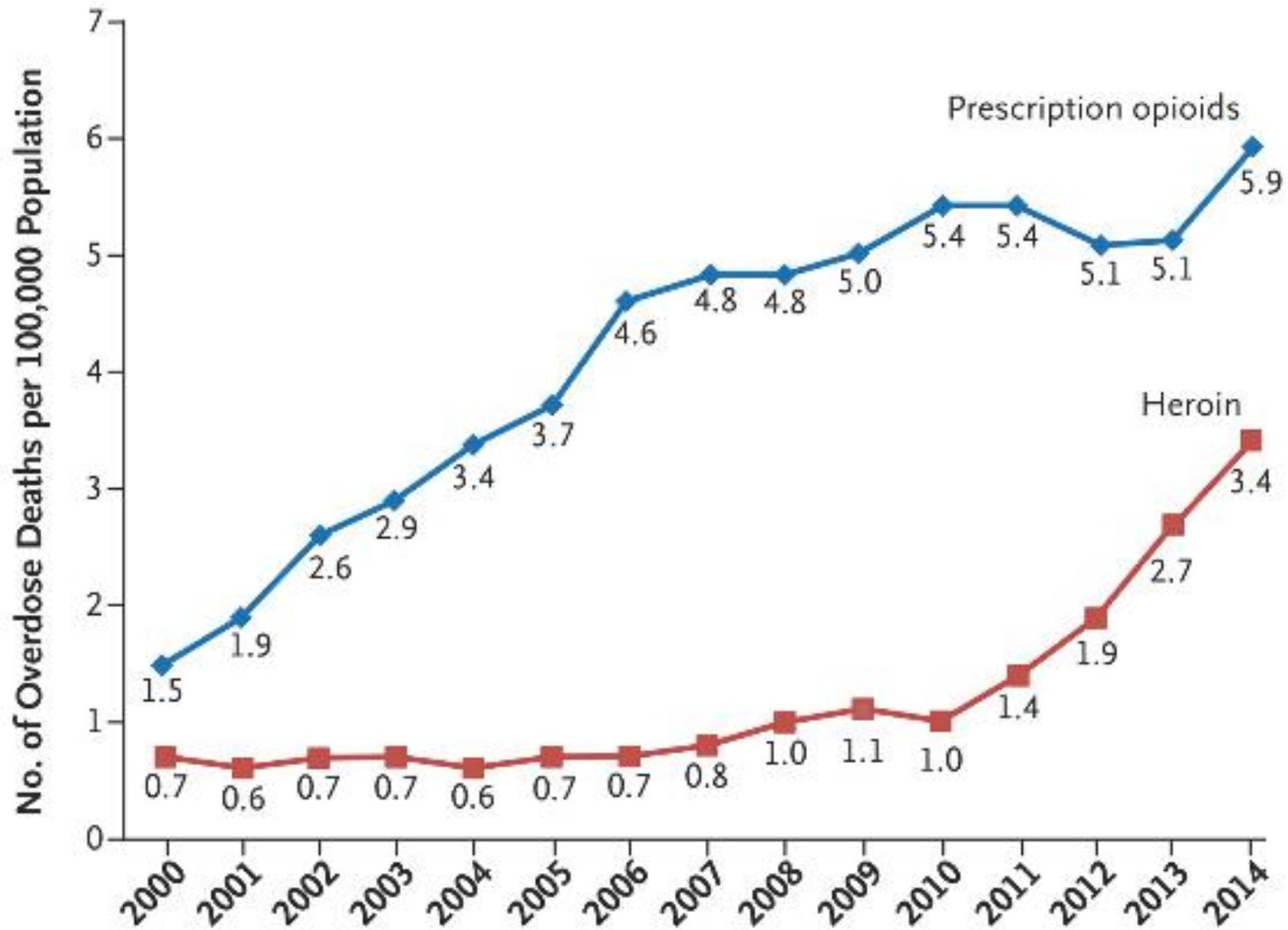
- 1996 – AMERICAN ACADEMY OF PAIN MEDICINE AND AMERICAN PAIN SOCIETY RELEASE CONSENSUS PAPER:
  - “**VERY LITTLE RISK OF ADDICTION OR OVERDOSE IN CHRONIC PAIN PATIENTS**”.
- 1996 –PURDUE PHARMA RELEASES **OXYCONTIN**.
- 2001 – PAIN BECOMES THE “FIFTH VITAL SIGN”.
- 2001 – FEDERATION OF STATE MEDICAL BOARDS REASSURES DOCTORS THEY WON'T FACE ACTION FOR PRESCRIBING LARGE AMOUNTS OF OPIOIDS
- 2004 – FEDERATION OF STATE MEDICAL BOARDS URGES STATES TO **MAKE UNDER-TREATMENT OF PAIN PUNISHABLE** FOR THE FIRST TIME



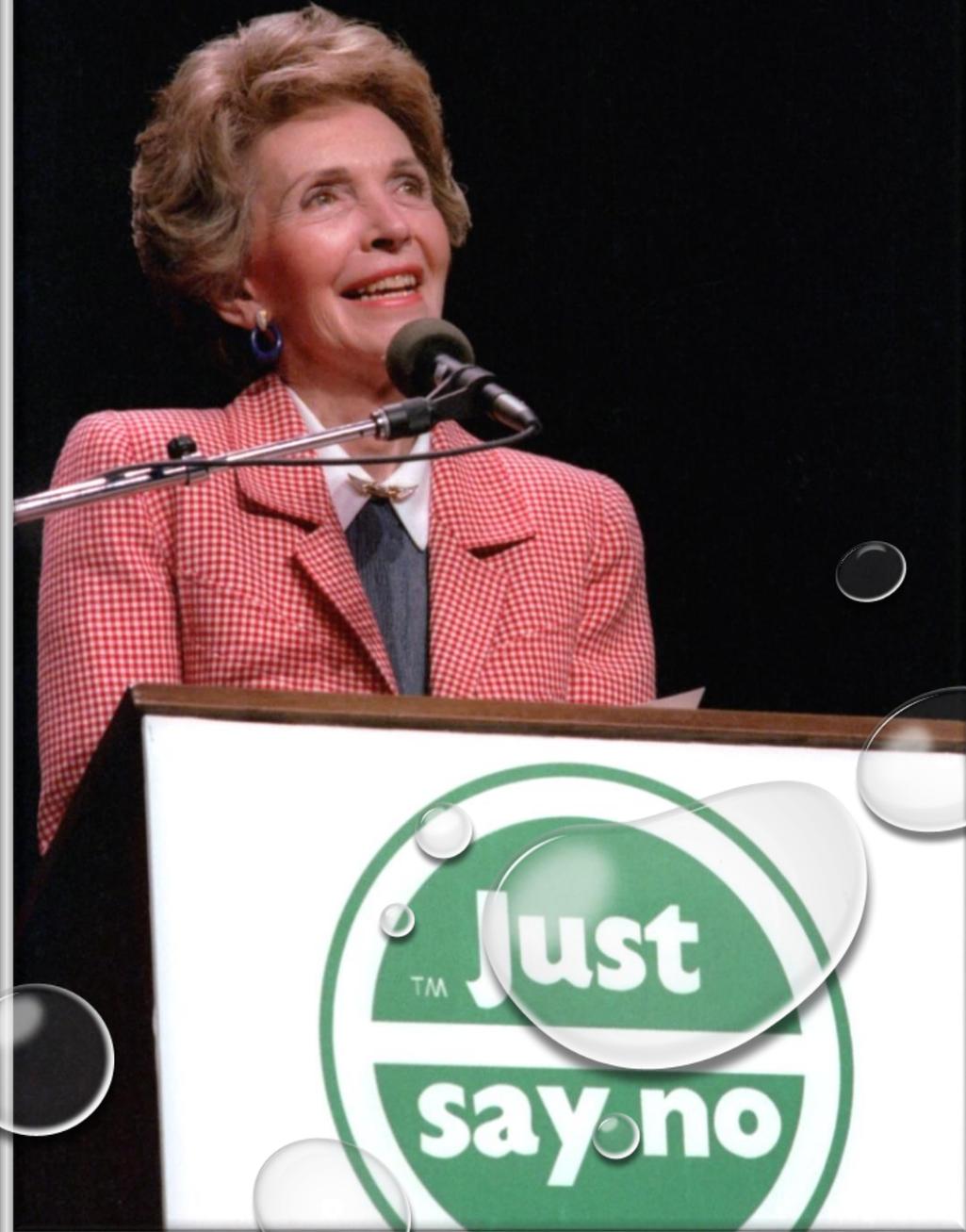
# Figure 4. Opioid Prescriptions Dispensed by US Retail Pharmacies



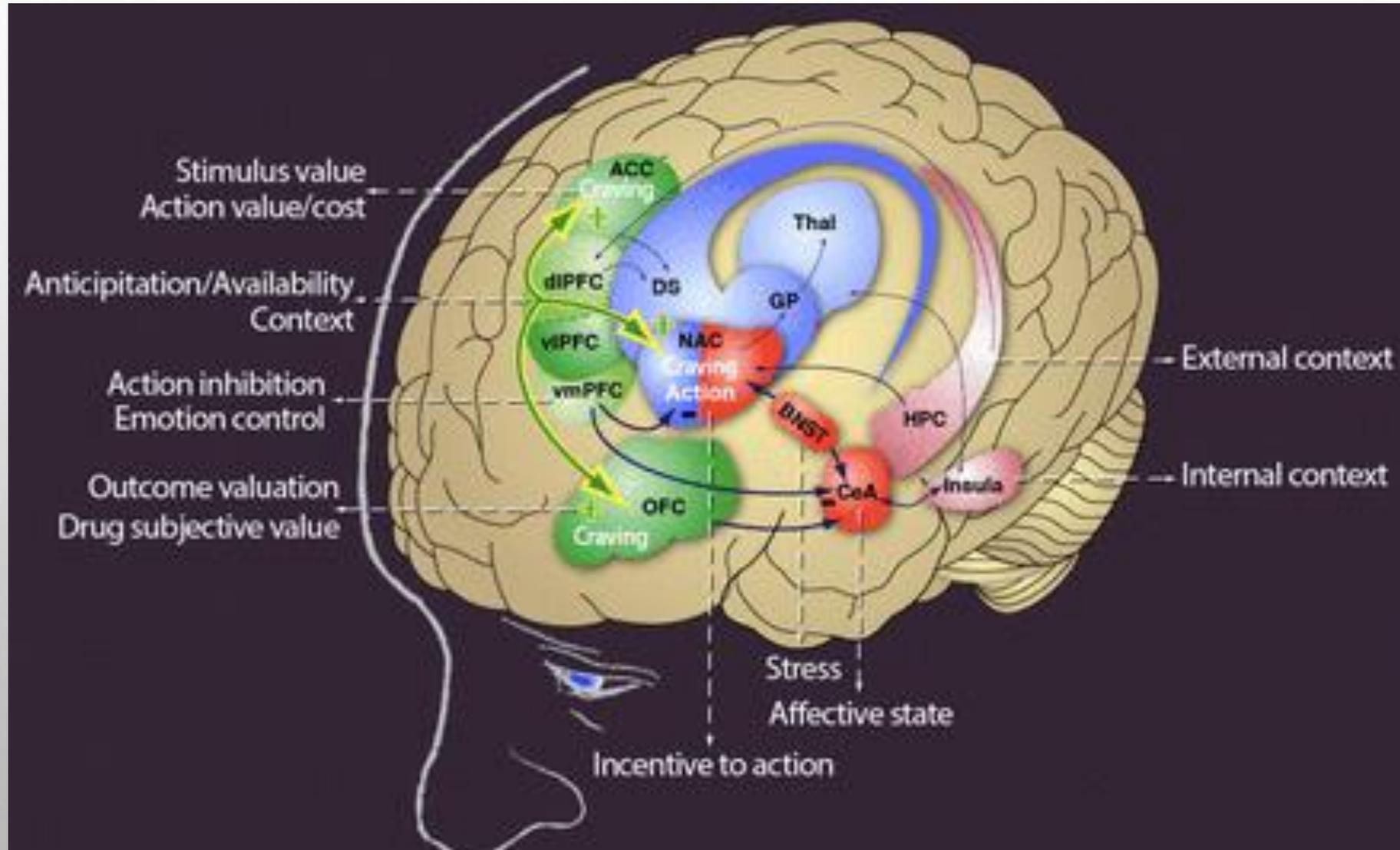
Source: IMS Vector One® National (VONA)



WHY  
DON'T  
THEY JUST  
STOP?



# ADDICTION IS A BRAIN DISEASE



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.

~American Society of Addiction Medicine

# WHAT ADDICTION IS NOT.

- **TOLERANCE** – THE NEED FOR MORE DRUG TO ACHIEVE THE SAME EFFECT
- **DEPENDENCE** – PHYSICAL CHANGES FROM REPEATED EXPOSURE SUCH THAT DISCONTINUATION RESULTS IN WITHDRAWAL.
- **PSEUDOADDICTION** -PATTERN OF DRUG SEEKING BEHAVIOR RESULTING FROM INADEQUATELY TREATED PAIN (RESOLVES WITH ADEQUATE ANALGESIA)

# THE 4 C'S (+ 1)

- CRAVING
- COMPULSION
- LOSS OF CONTROL
- CONTINUED USE IN SPITE OF NEGATIVE CONSEQUENCES.
- PERSISTENT NEGATIVE AFFECT

Addiction	Pseudoaddiction
Losing prescriptions. Asking for opioid replacements.	May use other available drugs to treat symptoms; excessive acetaminophen or NSAID use, burns from heating pads, benadryl to sleep, etc.
Calling at night or on weekend for refills/additional meds – wants to get medical provider partner who doesn't know them; may call office to ask who is on for the weekend.	Typically calls during office hours, but could have pain exacerbate on off hours.
Sense of urgency – calls office multiple times in a day > 2 times. May show up at office.	Aggressive complaining about needing more drugs, but typically will only call office 1-2 times.
Obtaining opioids/benzodiazepines from multiple providers (won't tell you) – check state prescription report at initial visit.	May have several providers but WILL tell you who is prescribing what medication for what purpose.
Multiple allergies – explore, can skin test.	Requesting specific drugs – just knows what works from past exposure.
Refuses additional testing for pain complaints.	May be resistant to testing that has been done in past but ultimately will comply; may ask for additional testing.
Caught selling prescription drugs to get drug of choice, or forging prescriptions – changing “n” on prescription. Stealing drugs.	May borrow drugs from family members but will tell prescriber. Will not steal or forge prescription drugs.
Using drug by unprescribed route – snorting or injecting, chewing long-acting agents.	May be anxious about changes in medications or route for fear of being back in pain.
Concurrent abuse of other drugs will show up on tox screen. Other addictions present.	Tox screen negative for other illicit drugs.
Repeatedly escalating dose despite warnings.	Occasionally escalates drug dose but will let you know.
Frequent ED visits WITHOUT telling prescriber.	May visit ED but WILL tell doctor to convince him/her that problems exist.
Making up or embellishing chronic diagnoses; reluctant to give the previous physician's name or number.	Willingly provides paperwork and physician name for other diagnoses.
Exhibits work, family, social deterioration. Unemployed or frequent job changes.	May temporarily not be working unless disabled, but often employed.

# DSM-V SUBSTANCE USE DISORDER

- 2-3 MILD

- 4-5 MODERATE

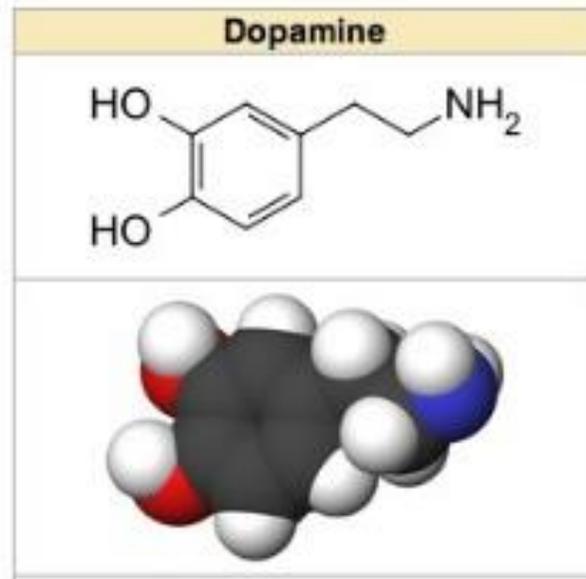
- 6+ SEVERE

- Tolerance
- Withdrawal
- Taken more/longer than intended
- Desire/unsuccessful efforts to quit use
- Great deal of time taken by activities involved in use
- Use despite knowledge of problems associated with use
- Important activities given up because of use
- Recurrent use resulting in a failure to fulfill important role obligations
- Recurrent use resulting in physically hazardous behavior (e.g., driving)
- Continued use despite recurrent social problems associated with use
- Craving for the substance

# Overview

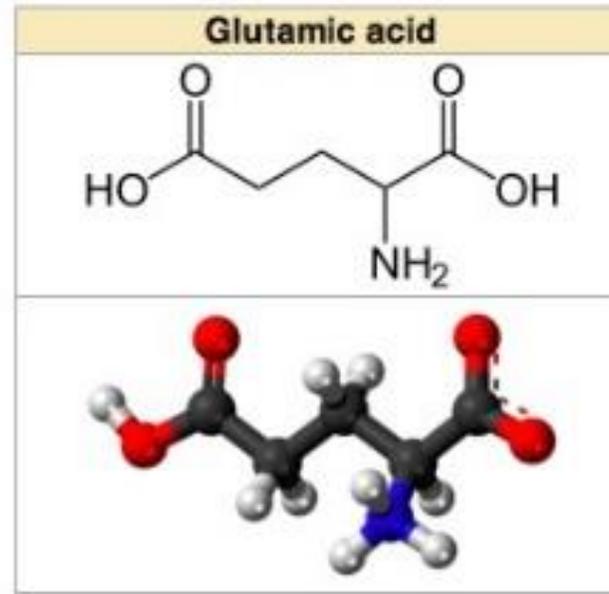
## Dopamine

Pleasure +  
Motivation



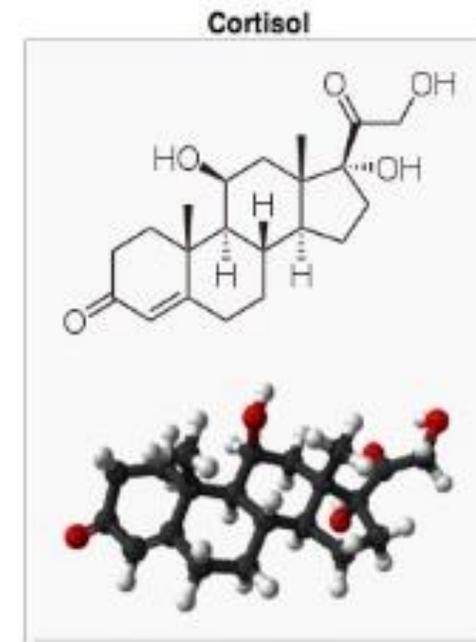
## Glutamate

Plasticity +  
Potentiation



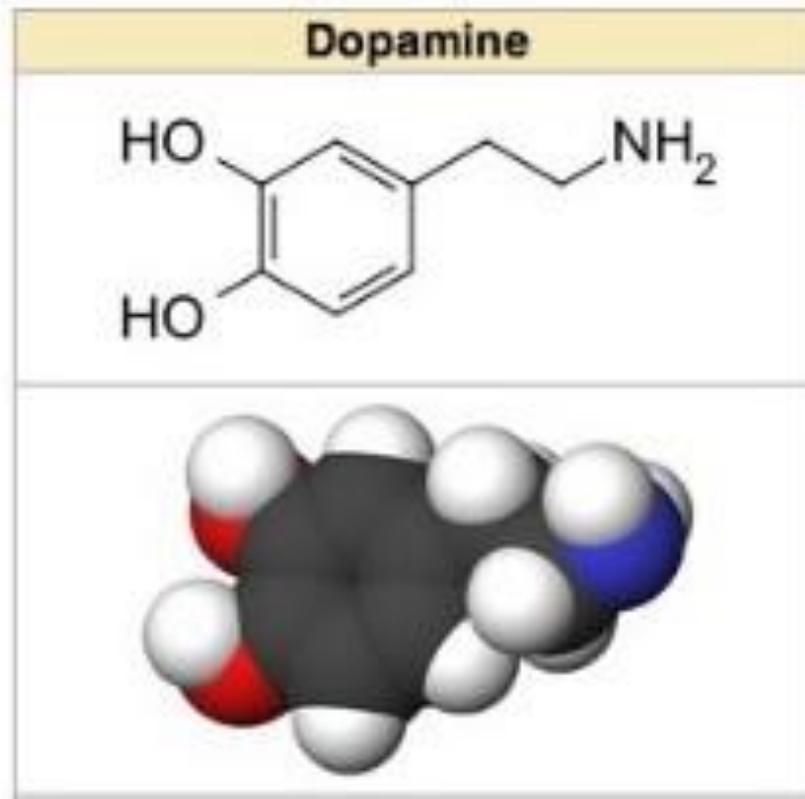
## Corticosteroids

Stress



# Dopamine

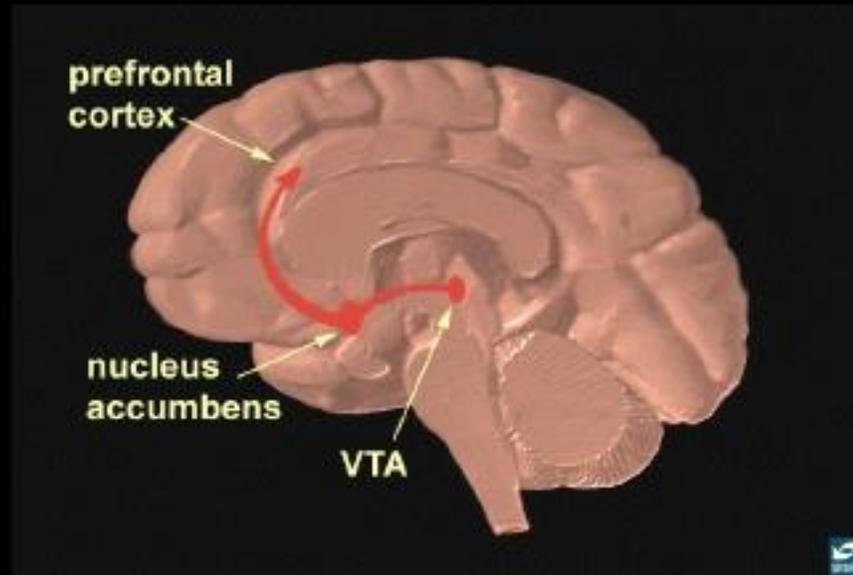
Pleasure +  
Motivation



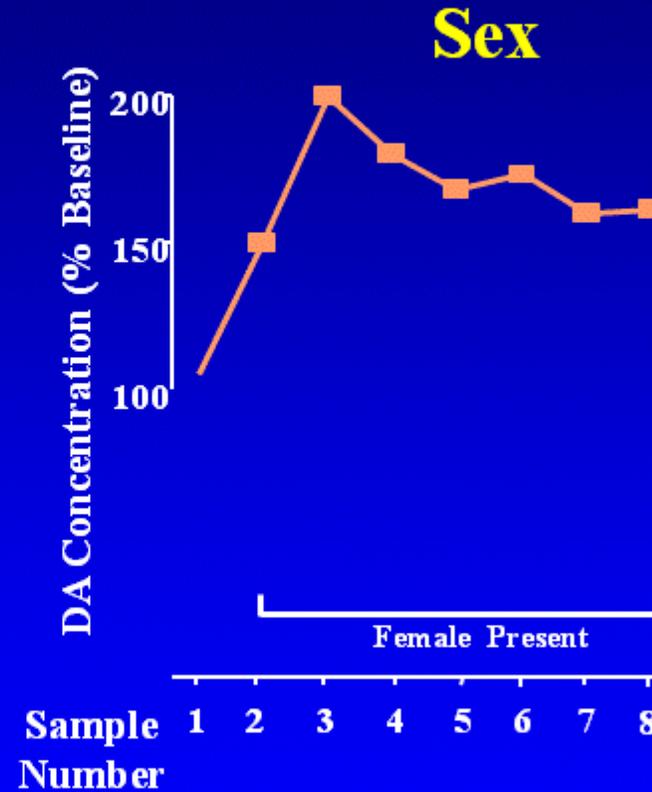
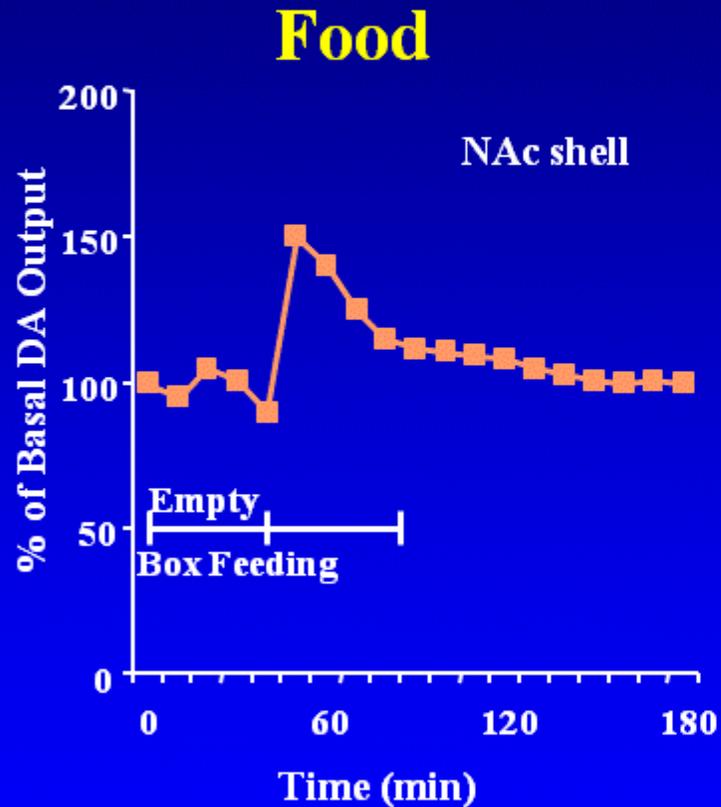


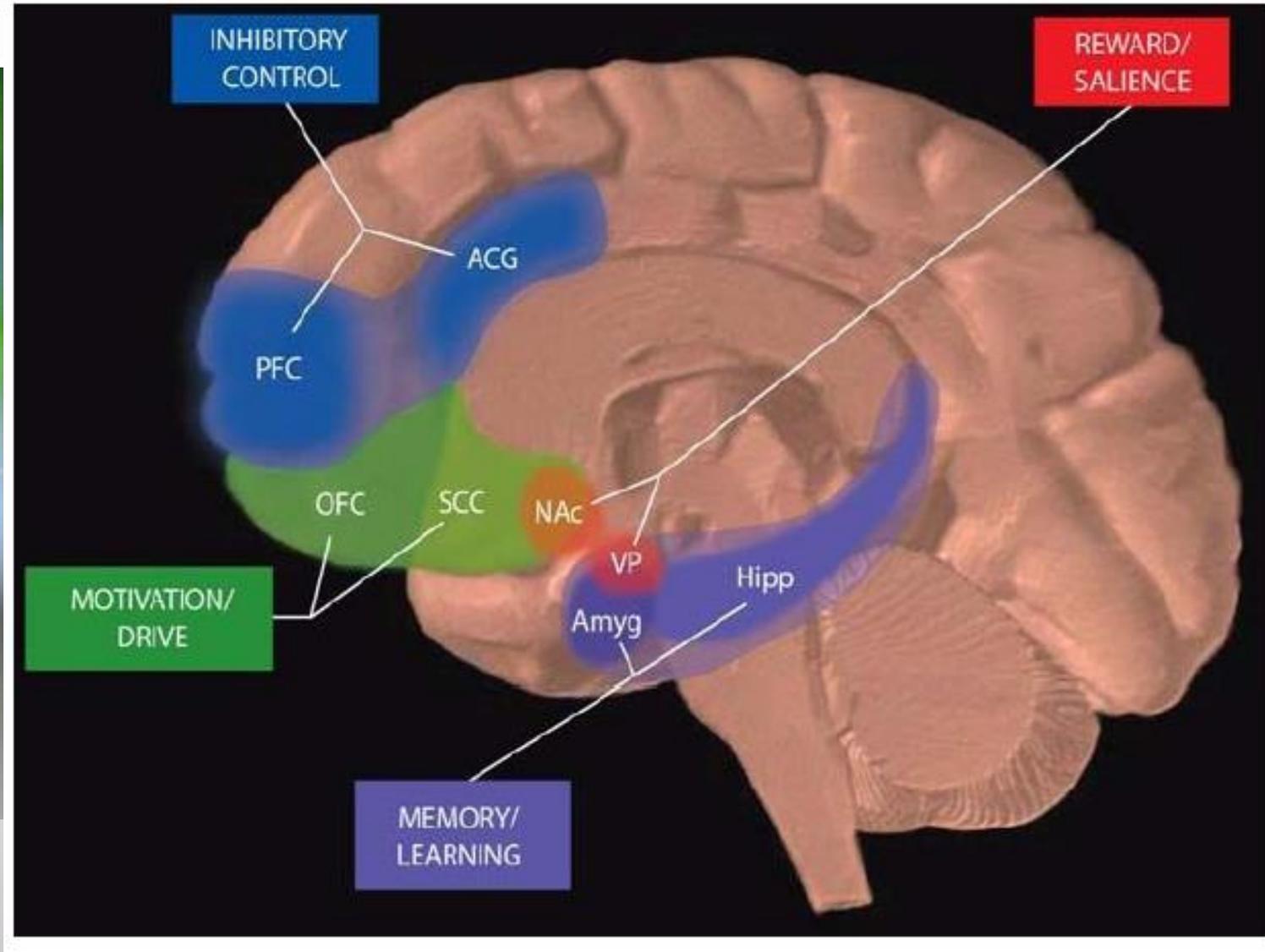
# Reward Pathway

- Stimulated normally by food, sex, water, etc.
- VTA (ventral tegmental area) connects to the nucleus accumbens and prefrontal cortex
- Neurons in VTA contain dopamine, which is released in the nucleus accumbens and prefrontal cortex in response to the rewarding stimulus



# Natural Rewards Elevate Dopamine Levels

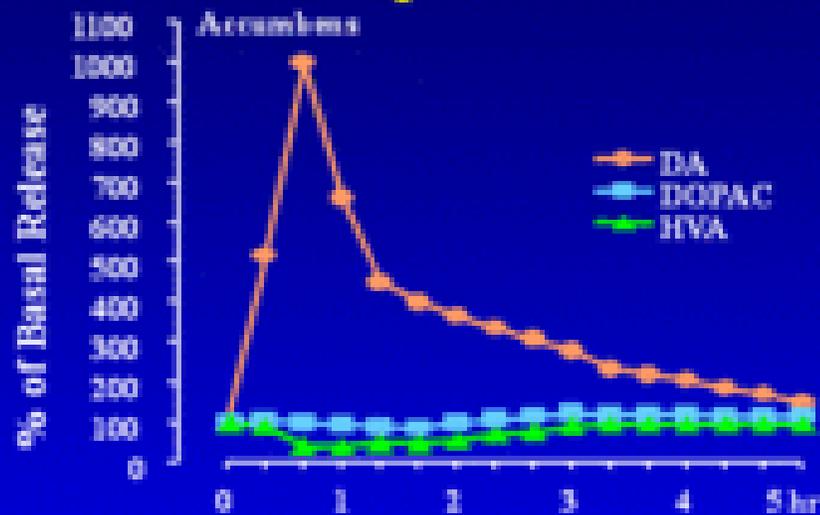




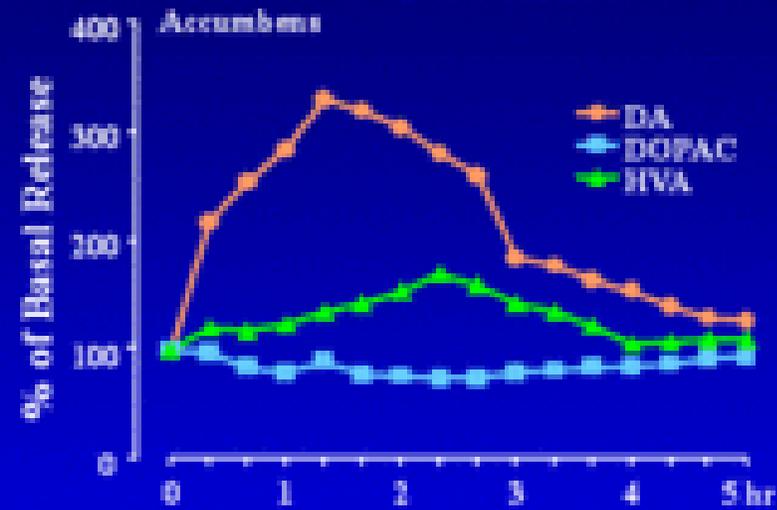


# Effects of Drugs on Dopamine Release

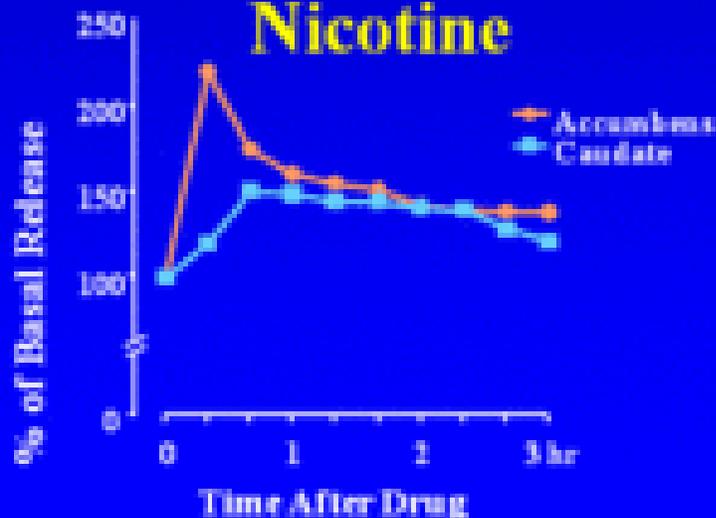
## Amphetamine



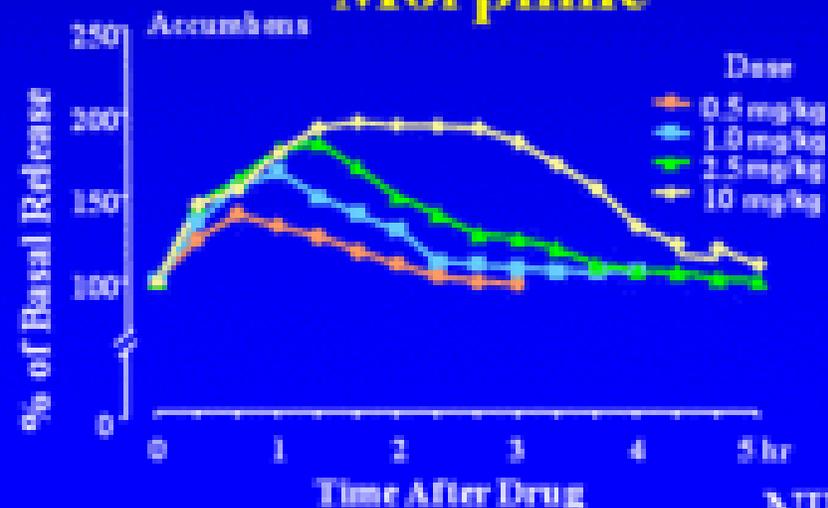
## Cocaine

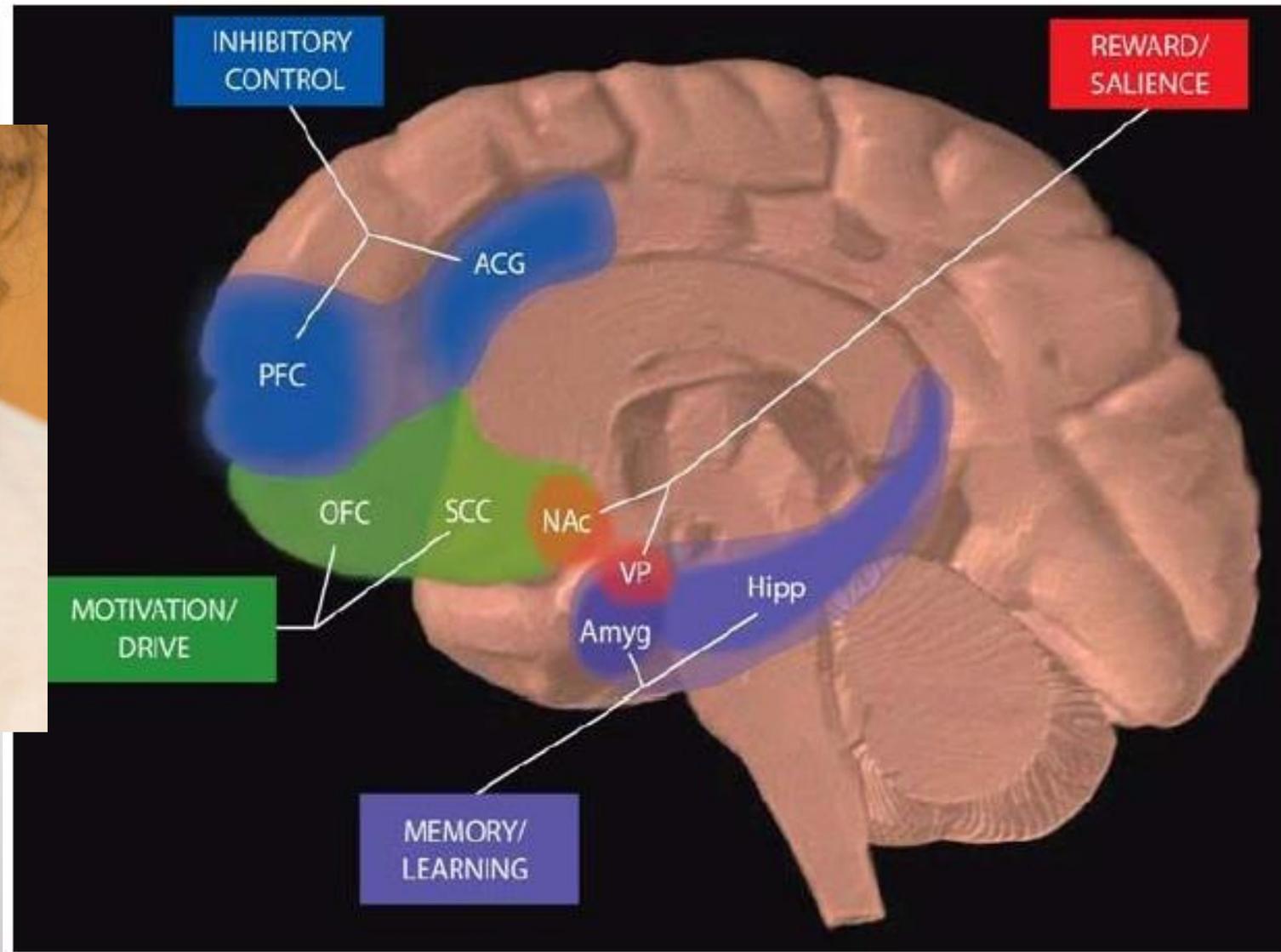


## Nicotine

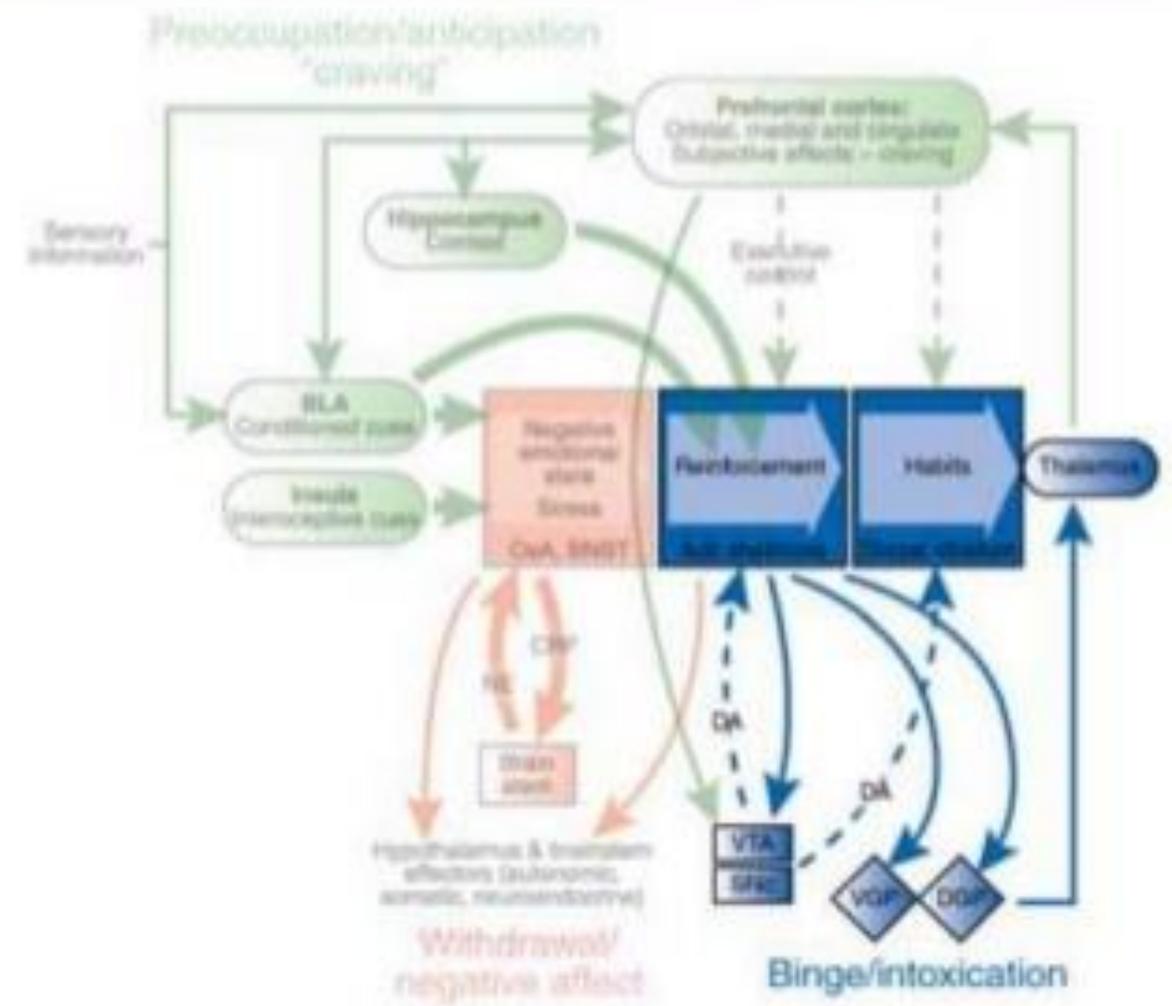
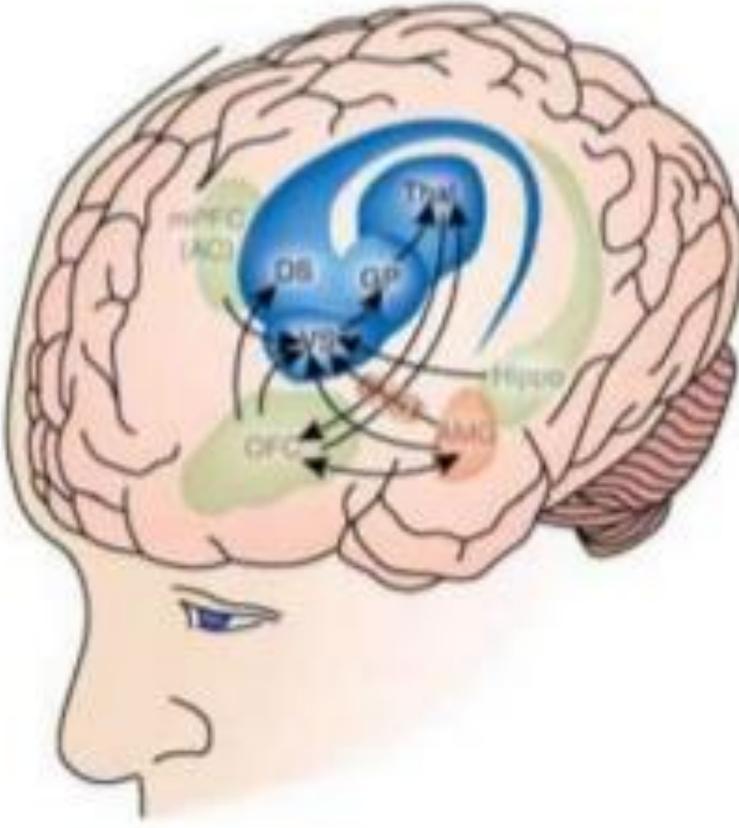


## Morphine



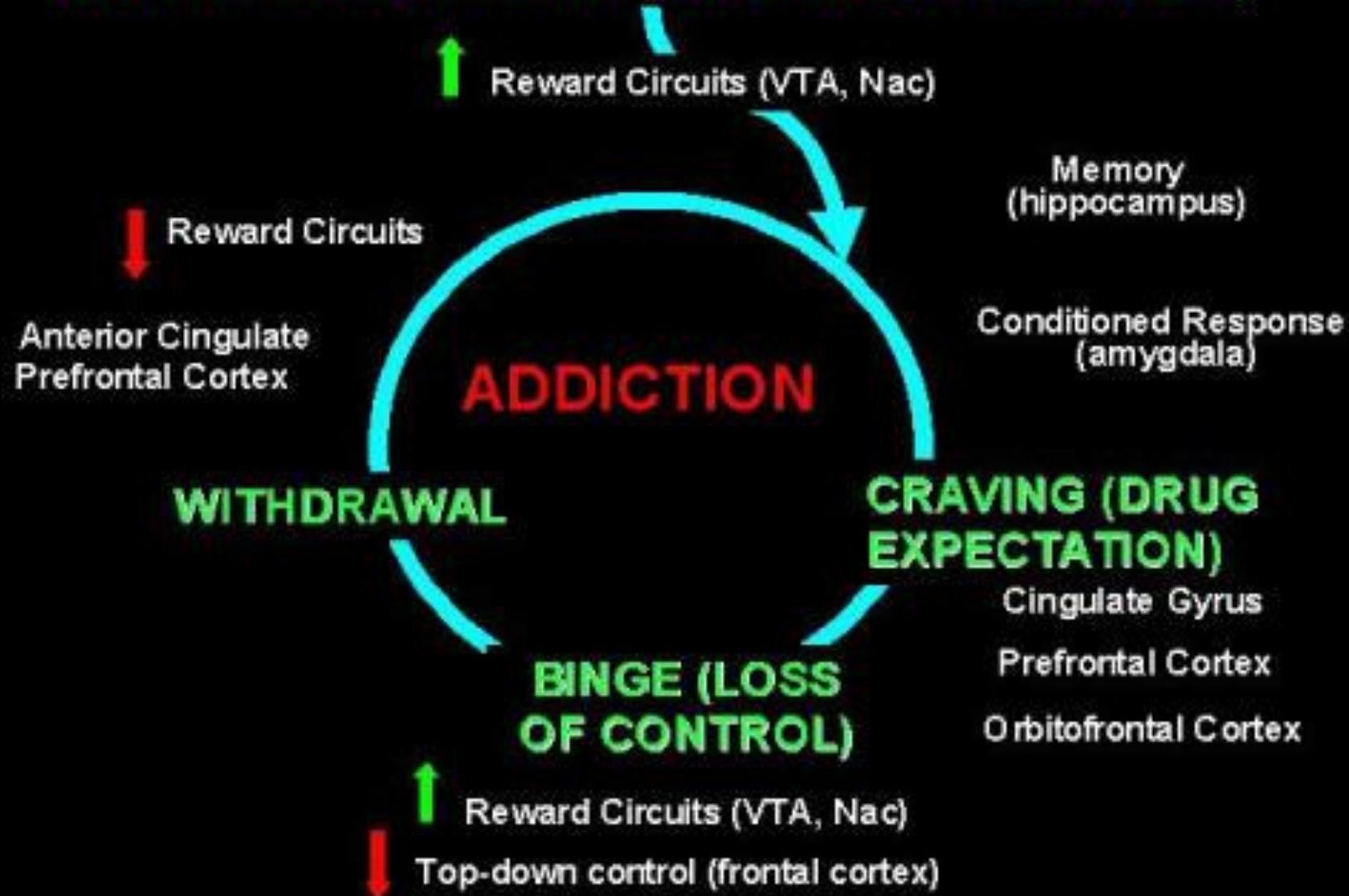


a



**Binge/intoxication stage:** Reinforcing effects of drugs may engage reward neurotransmitters and associative mechanisms in the Nucleus Accumbens shell and core and then engage stimulus–response habits that depend on the dorsal striatum. Two major neurotransmitters mediating the rewarding effects of drugs of abuse are **dopamine** and **opioid** peptides.

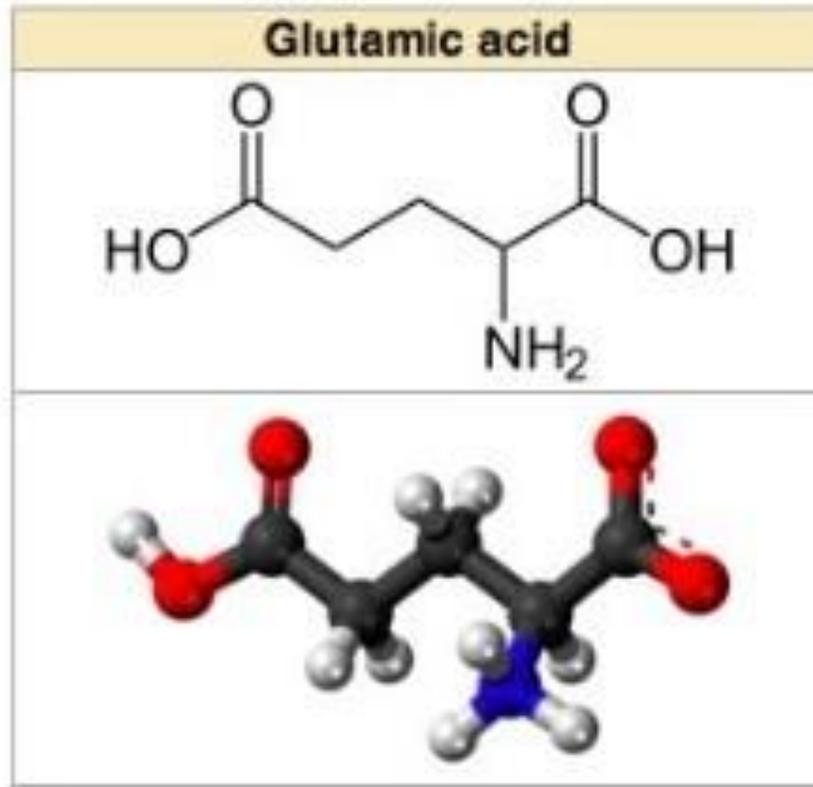
# DRUG REINFORCEMENT (SALIENCE ATTRIBUTION)



# Glutamate

Plasticity +

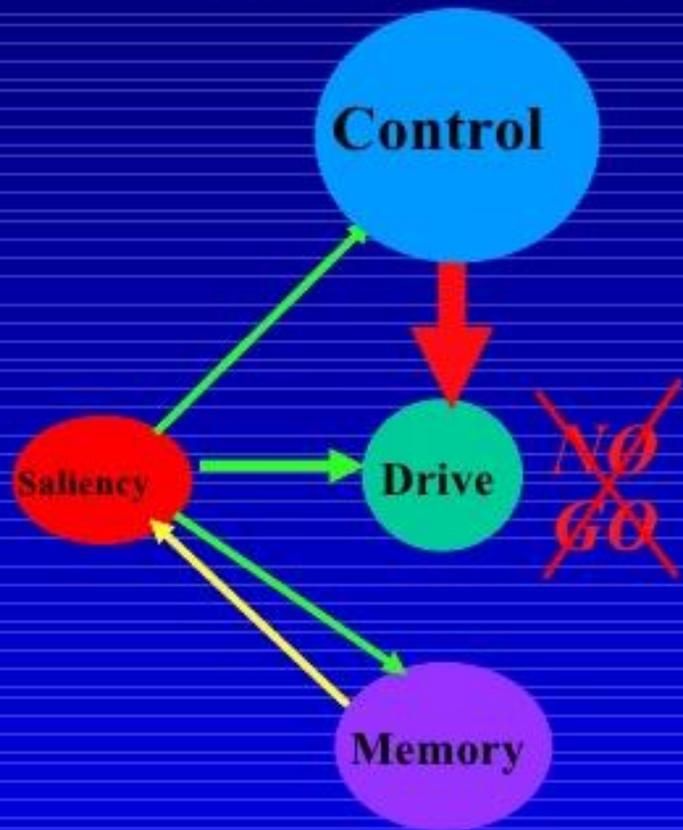
Potentialiation



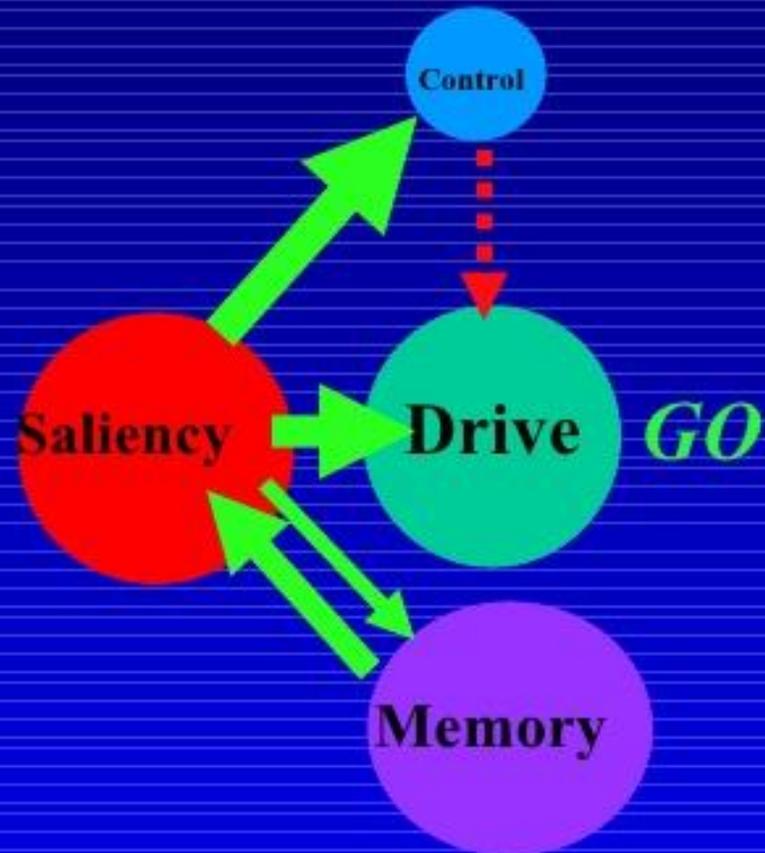


# Why Can't Addicts Just Quit?

Non-Addicted Brain



Addicted Brain

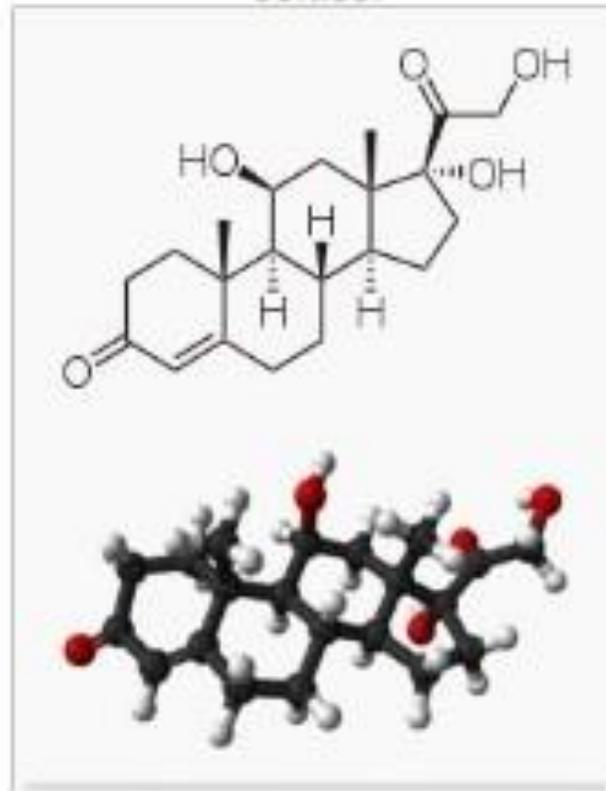


*Because Addiction Changes Brain Circuits*

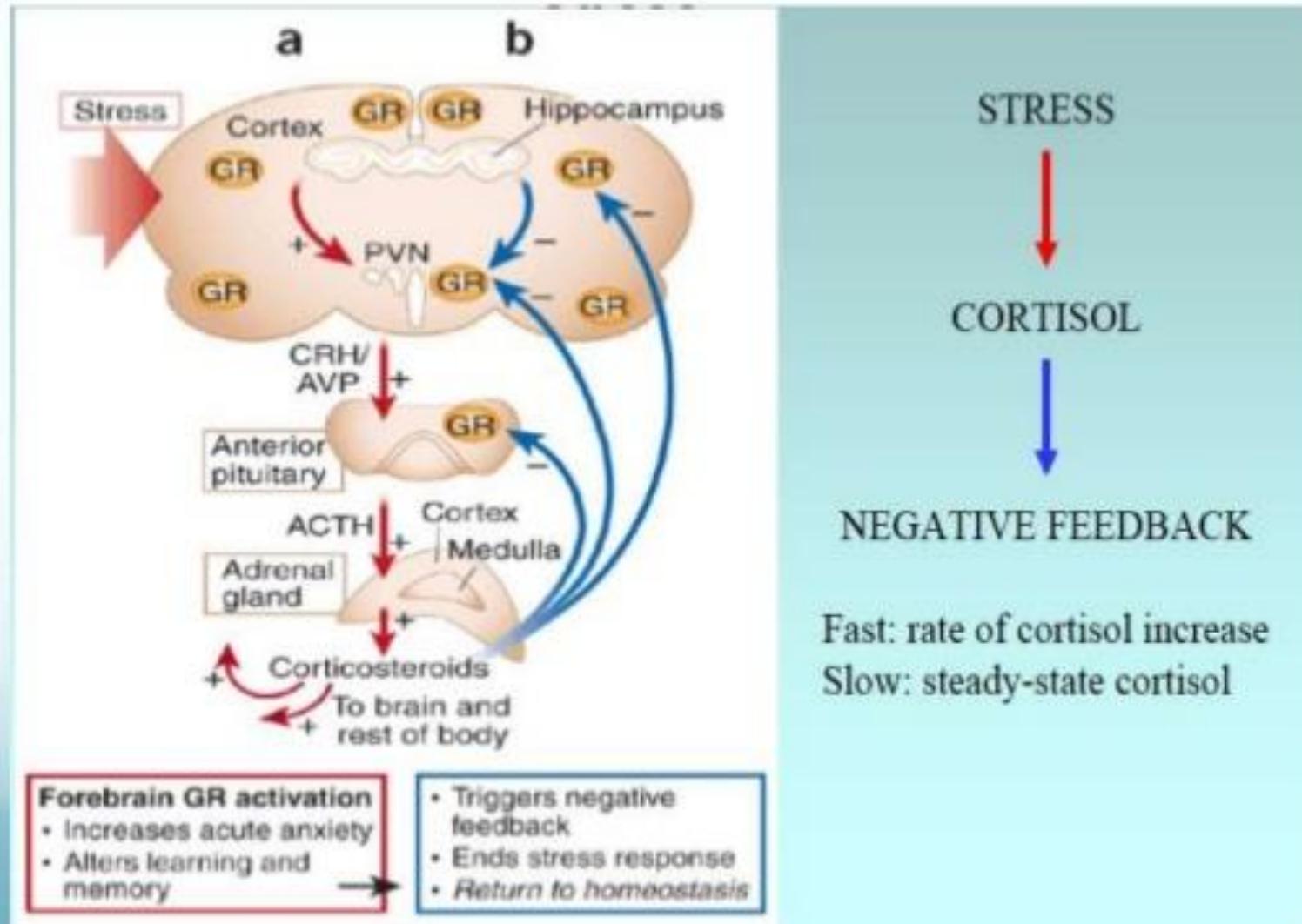
# Corticosteroids

## Stress

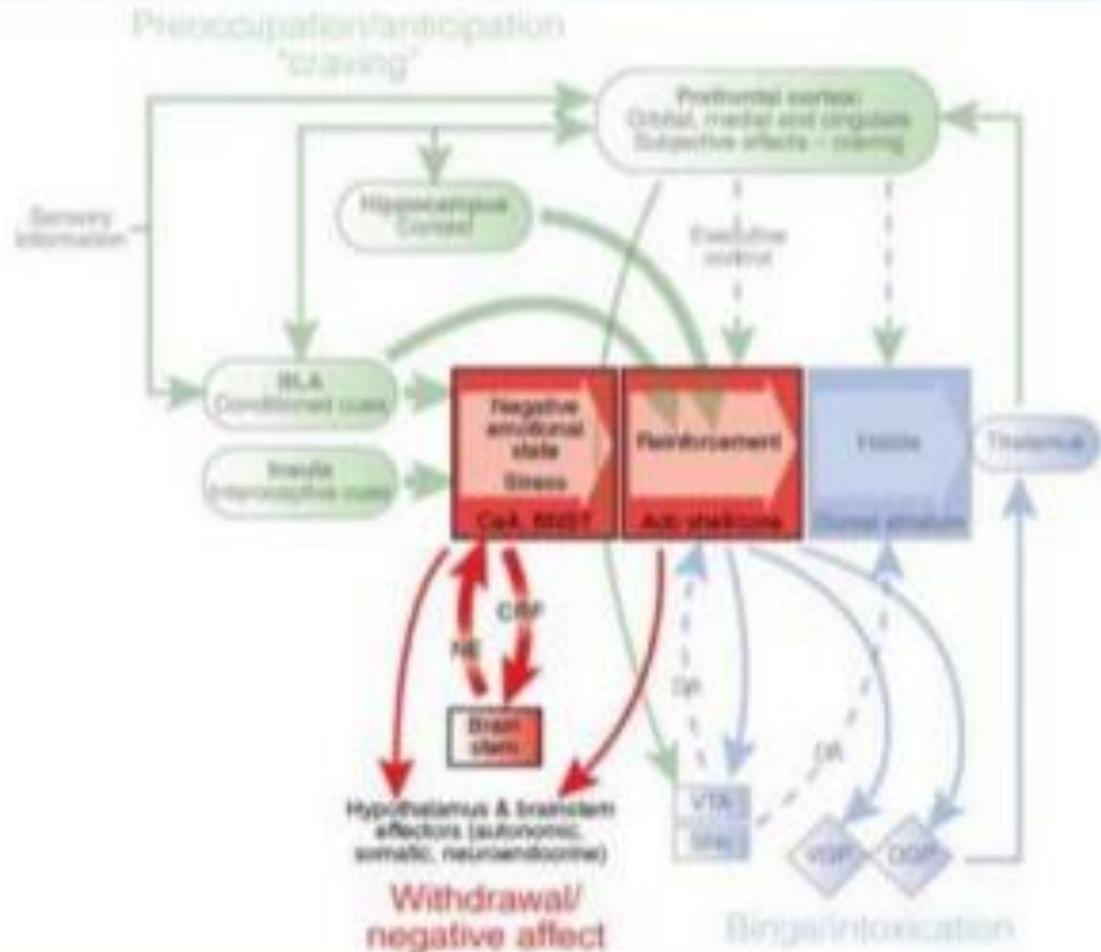
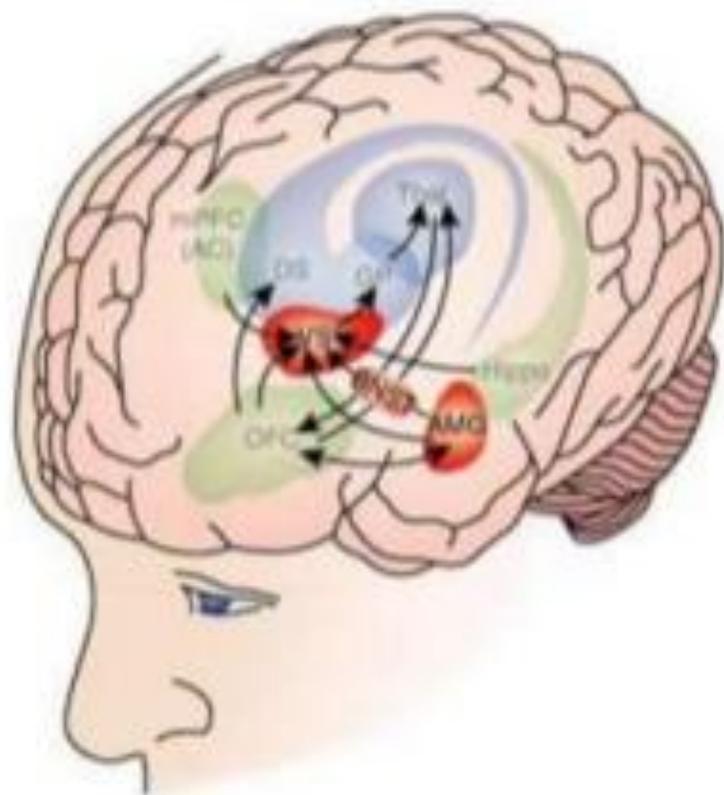
**Cortisol**



# HPA Axis Activation and Negative Feedback

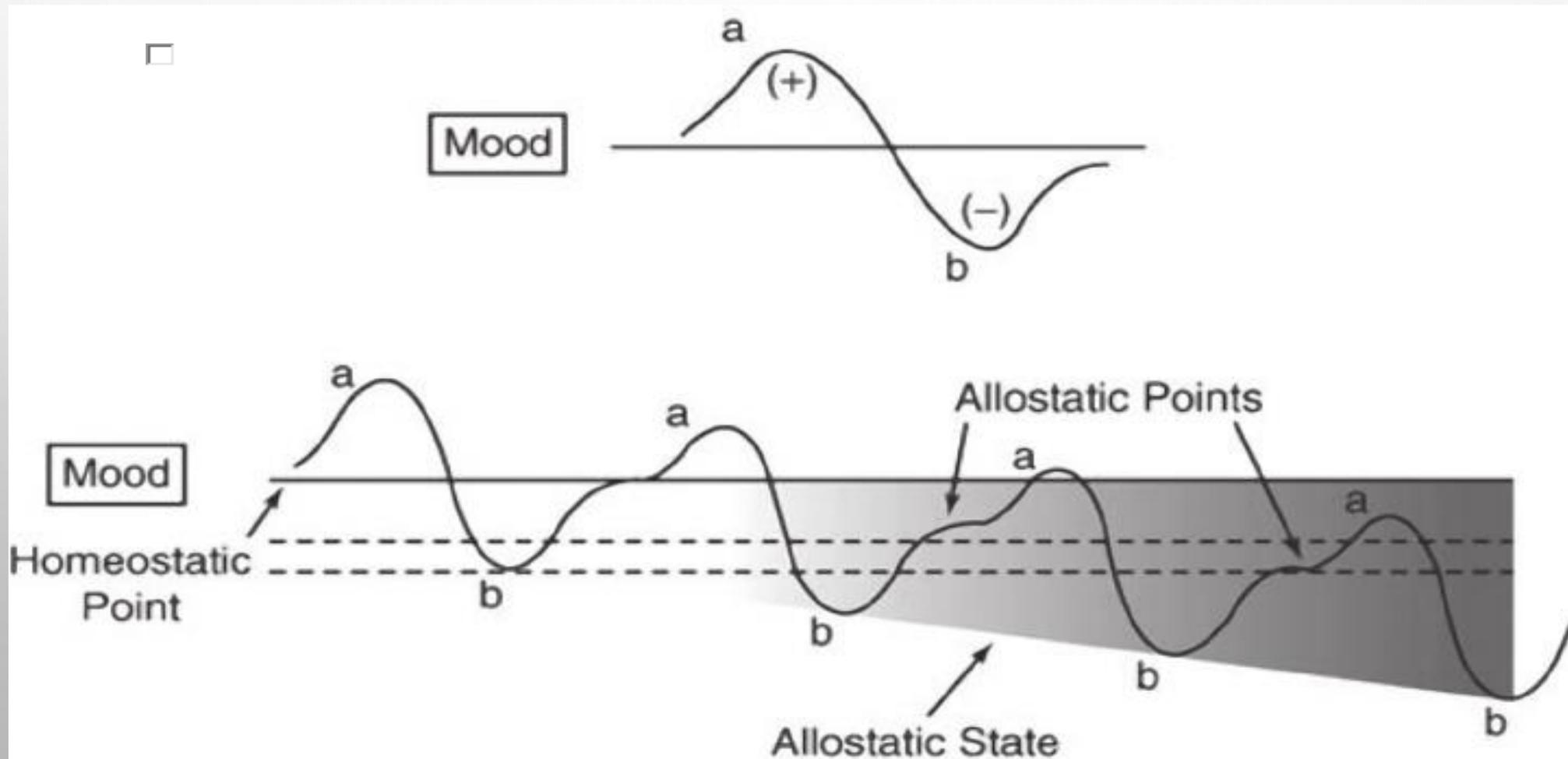


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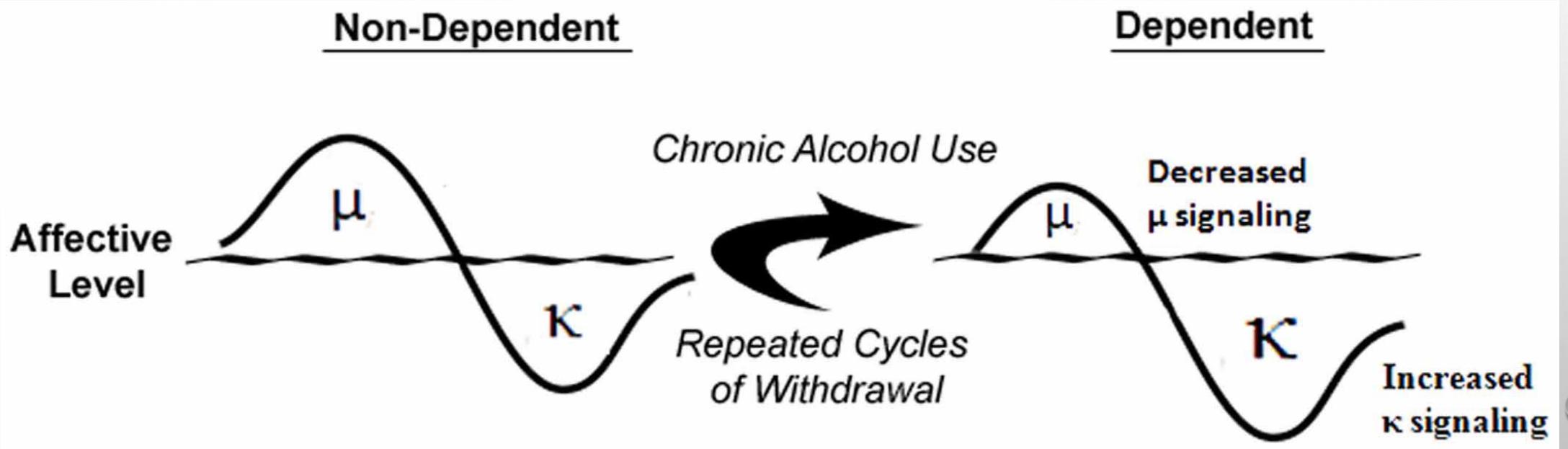


The negative emotional state of withdrawal may engage the activation of the **extended amygdala**. Major neurotransmitters in the extended amygdala hypothesized to have a function in negative reinforcement are **corticotropin-releasing factor**, **norepinephrine**, and **dynorphin**. Major projections of the extended amygdala are to the **hypothalamus** and **brainstem**.

# THE ANTI-REWARD SYSTEM



# KAPPA OPIOID RECEPTOR/ DYNORPHIN MEDIATES OPPONENT PROCESS



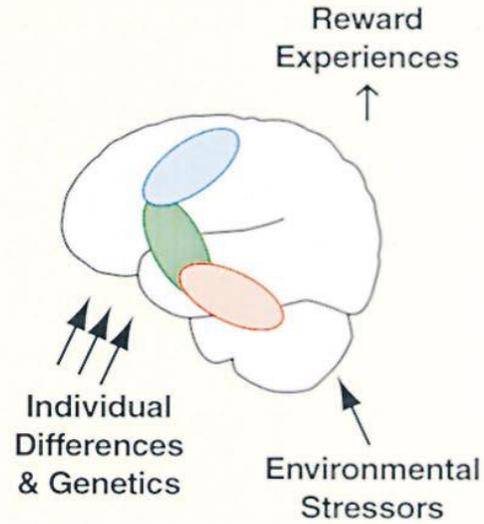
## Drug Reward Non-Dependent

## Transition to Dependence

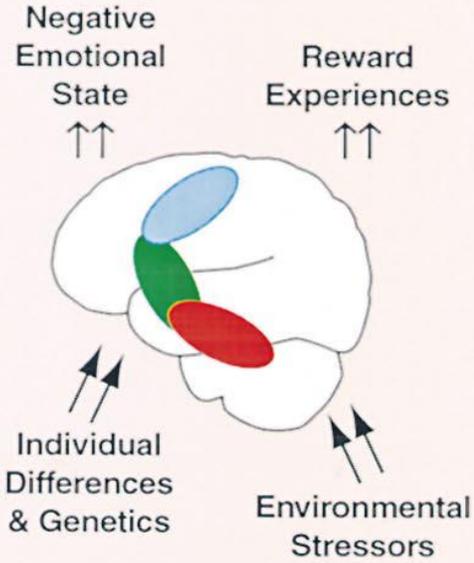
## Addiction

## Protracted Abstinence

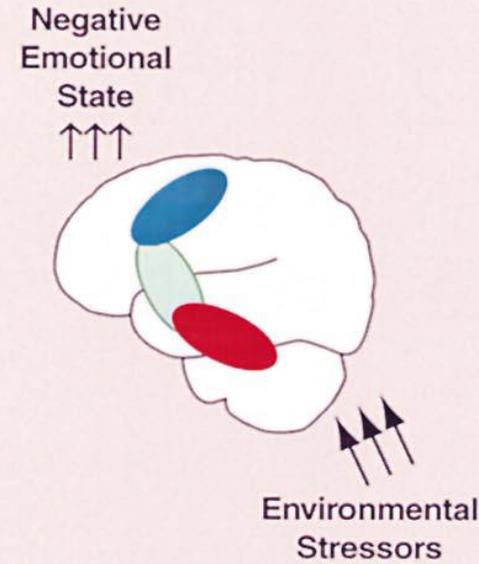
- Cort-Thal-Striat loop
- Brain reward system
- Brain stress system



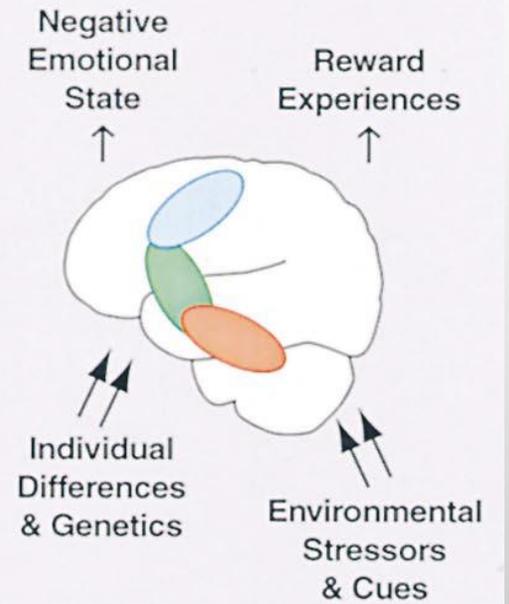
DA ↑  
 Glucocorticoids ↑  
 GR Sensitivity ↓↓  
 CRF ↑



DA ↑↑  
 Glucocorticoids ↑↑  
 GR Sensitivity ↓  
 CRF ↑↑



DA ↓↓  
 Glucocorticoids ↑↑↑  
 GR Sensitivity ↑?  
 CRF ↑↑↑



DA ↓  
 Glucocorticoids ↑↓  
 GR Sensitivity ↑↑  
 CRF ↑

Allostasis



Allostatic State



Allostatic Load (Pathology)

↑ Corticotropin-releasing factor

↑ Norepinephrine

↑ Dynorphin

↑ Vasopressin

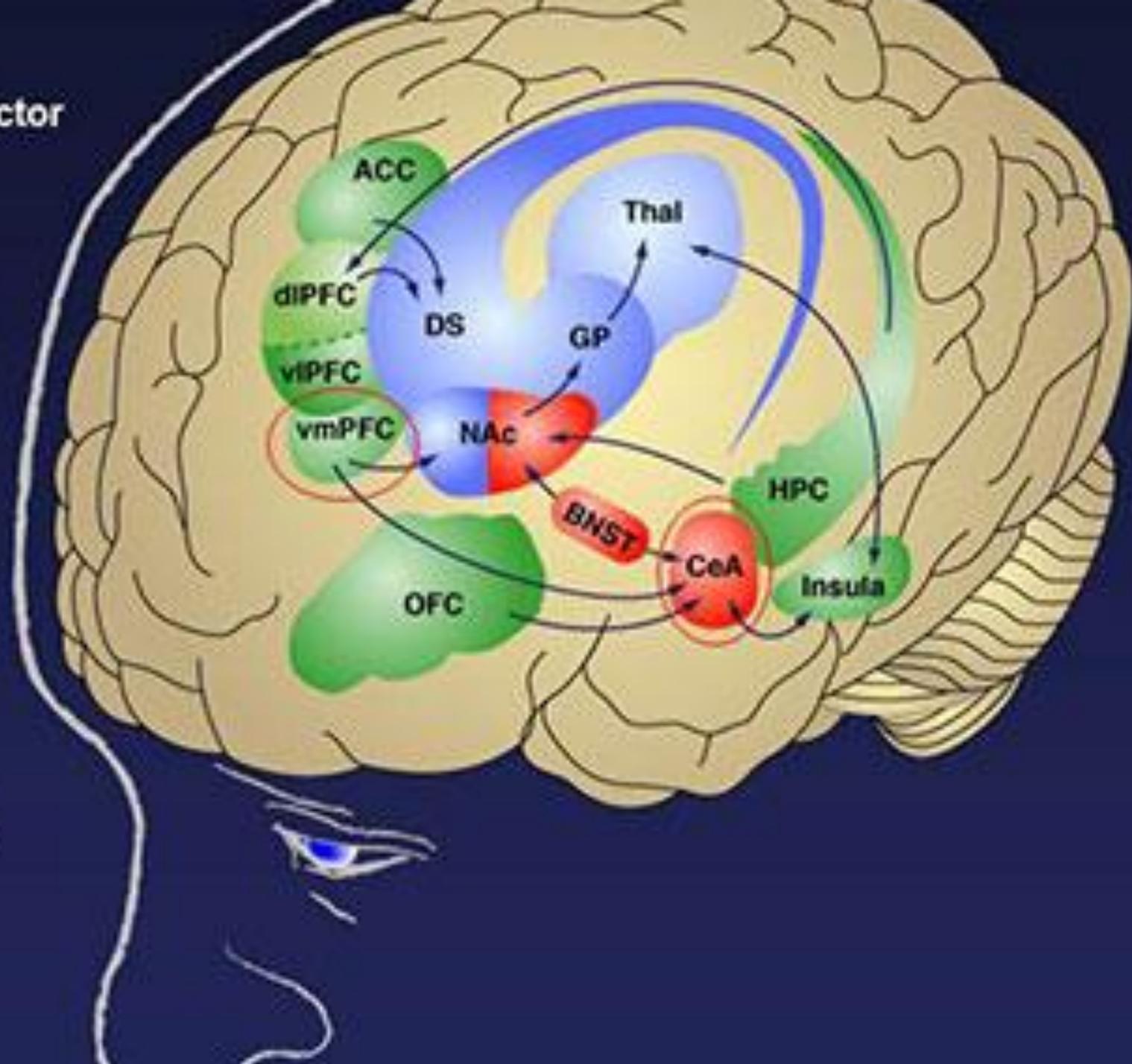
↑ Orexin (hypocretin)

↑ Substance P

↓ Neuropeptide Y

↓ Nociceptin (orphanin FQ)

↓ Endocannabinoids





# RISK FACTORS FOR ADDICTION

- **GENETIC**
- **ENVIRONMENTAL**

# TREATMENT CONSIDERATIONS

- INCREASE DOPAMINE RECEPTORS
  - SOCIAL CONNECTIONS
  - SENSE OF ACCOMPLISHMENT
  - RECONNECTION WITH LOVED ONES
  - THERAPEUTIC RELATIONSHIP
  - MEDICALLY ASSISTED THERAPY
    - BUPRENORPHINE

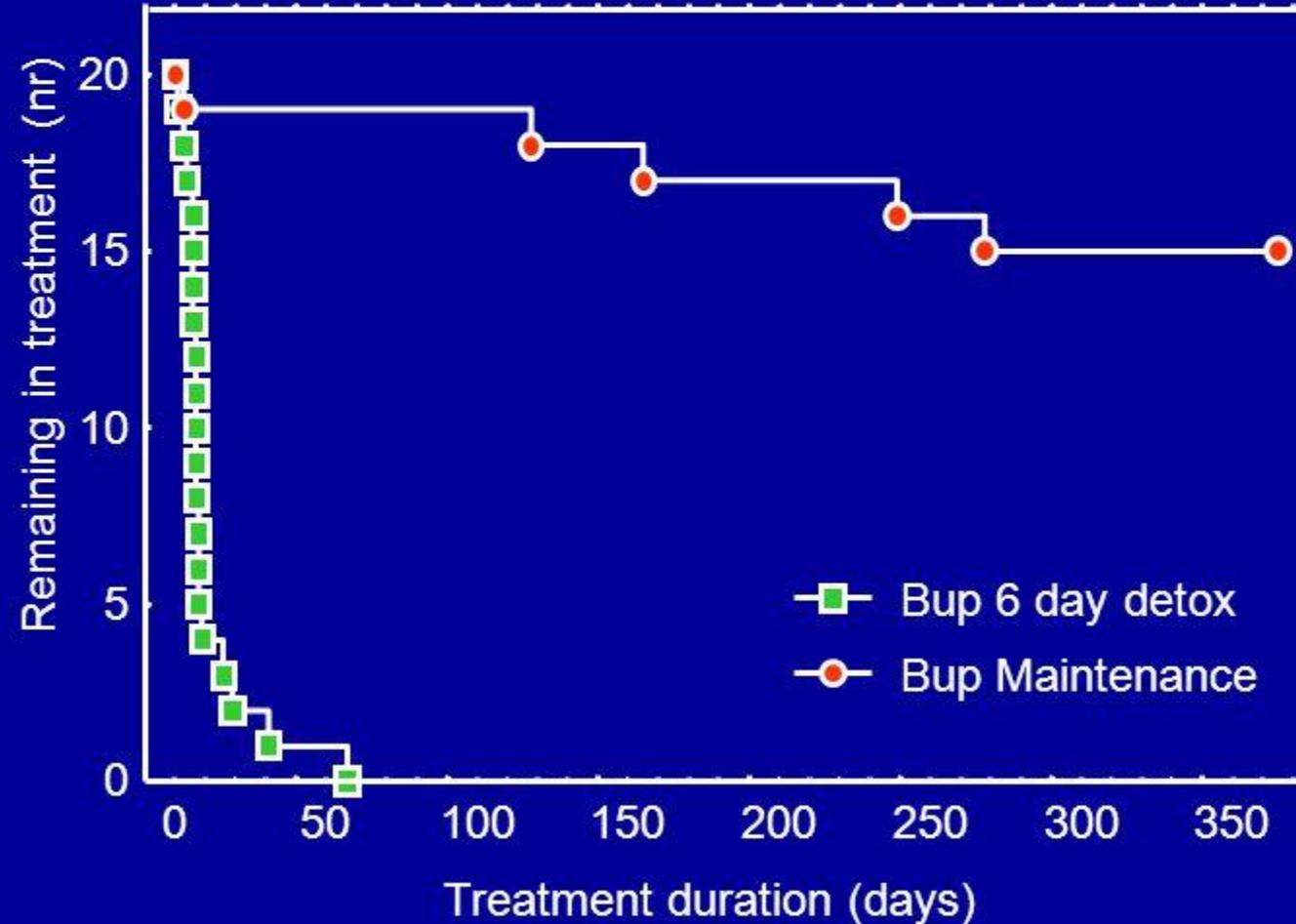
# TREATMENT CONSIDERATIONS

- DECREASE GLUTAMATE
  - GABAPENTIN
- DECREASE CRF ACTIVITY
  - BUPRENORPHINE – BLOCKS KAPPA RECEPTORS

# RCT: Bup Detox vs Maintenance

Kakko et al., Lancet 2003

All Patients: Group CBT Relapse Prevention, Weekly Individual Counseling, 3x Weekly Urine Screens



# RELAPSE RATE WITHOUT APPROPRIATE MAT



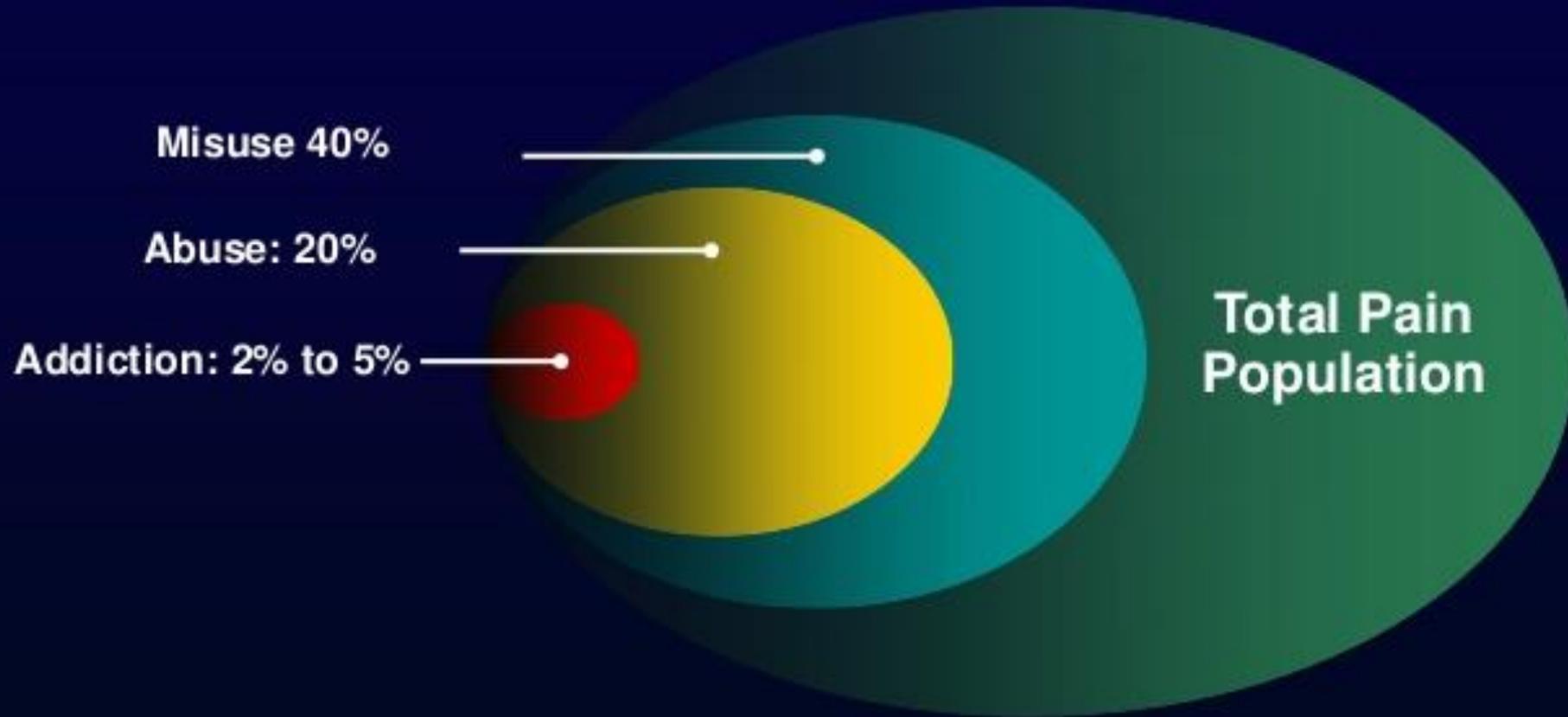


# CO-OCCURRING DISORDERS

- SOCIAL ANXIETY
  - PANIC DISORDER
  - DEPRESSION
  - PTSD
  - VICTIM OF SEXUAL ABUSE
  - BIPOLAR DISORDER
- 



# Prevalence of Misuse, Abuse, and Addiction





# 10 Principles of Universal Precautions

1. Diagnosis with appropriate differential
2. Psychological assessment including risk of addictive disorders
3. Informed consent (verbal or written/signed)
4. Treatment agreement (verbal or written/signed)
5. Pre-/post-intervention assessment of pain level and function
6. Appropriate trial of opioid therapy adjunctive medication
7. Reassessment of pain score and level of function
8. Regularly assess the "Four As" of pain medicine: *Analgesia, Activity, Adverse Reactions, and Aberrant Behavior*
9. Periodically review pain and comorbidity diagnoses, including addictive disorders
10. Documentation

# Risk Assessment Tools: Examples

Tool	# of items	Administered
<b>Patients considered for long-term opioid therapy:</b>		
<b>ORT</b> Opioid Risk Tool	5	By patient
<b>SOAPP</b> <sup>®</sup> Screener & Opioid Assessment for Patients w/ Pain	24, 14, & 5	By patient
<b>DIRE</b> Diagnosis, Intractability, Risk, & Efficacy Score	7	By clinician
<b>Characterize misuse once opioid treatments begins:</b>		
<b>PMQ</b> Pain Medication Questionnaire	26	By patient
<b>COMM</b> Current Opioid Misuse Measure	17	By patient
<b>PDUQ</b> Prescription Drug Use Questionnaire	40	By clinician
<b>Not specific to pain populations:</b>		
<b>CAGE-AID</b> Cut Down, Annoyed, Guilty, Eye-Opener Tool, Adjusted to Include Drugs	4	By clinician
<b>RAFFT</b> Relax, Alone, Friends, Family, Trouble	5	By patient
<b>DAST</b> Drug Abuse Screening Test	28	By patient
<b>SBIRT</b> Screening, Brief Intervention, & Referral to Treatment	Varies	By clinician

# OPIOID INDUCED HYPERALGESIA

- A STATE OF NOCICEPTIVE SENSITIZATION CAUSED BY EXPOSURE TO OPIOIDS. THE CONDITION IS CHARACTERIZED BY A PARADOXICAL RESPONSE WHEREBY A PATIENT RECEIVING OPIOIDS FOR THE TREATMENT OF PAIN COULD ACTUALLY BECOME MORE SENSITIVE TO CERTAIN PAINFUL STIMULI
- OPIOIDS START MAKING THE PAIN WORSE, NOT BETTER.

# Suggested Clinical Criteria for Diagnosing OIH

- Increased pain intensity during ongoing opioid treatment
- No evidence for underlying disease progression
- No evidence for either clinical or pharmacological opioid withdrawal
- No evidence for tolerance: to be tested by decreased pain in response to adequate opioid rescue dose
- Decrease in pain intensity in response to reduction in opioid dose
- No evidence for addictive behavior



# PROPOSED MECHANISMS OF OIH

- NDMA
  - RECEPTOR UPREGULATION
  - INCREASED GLUTAMATE
- DYNORPHIN
  - INCREASED LEVELS IN SPINE
  - MEDIATED BY INCREASED CCK RELEASE IN RVM (ROSTRAL VENTRAL MEDULLA)
- PROSTAGLANDINS
  - INCREASED PAIN SIGNALING IN SPINAL CORD

# TREATMENT OF OIH

- OPIOID WEANING
- NON OPIOID THERAPIES
  - INTERVENTIONAL PAIN MANAGEMENT
  - ANTIDEPRESSANTS
  - ANTICONVULSANTS
  - COUNSELING (CBT)
- OPIOIDS WITH UNIQUE PROPERTIES
  - METHADONE
  - BUPRENORPHINE
- NMDA AGONISTS
  - KETAMINE
  - DEXTROMETHORPHAN
- COX-2 INHIBITORS

# SUBSTANCE INDUCED MOOD DISORDER

