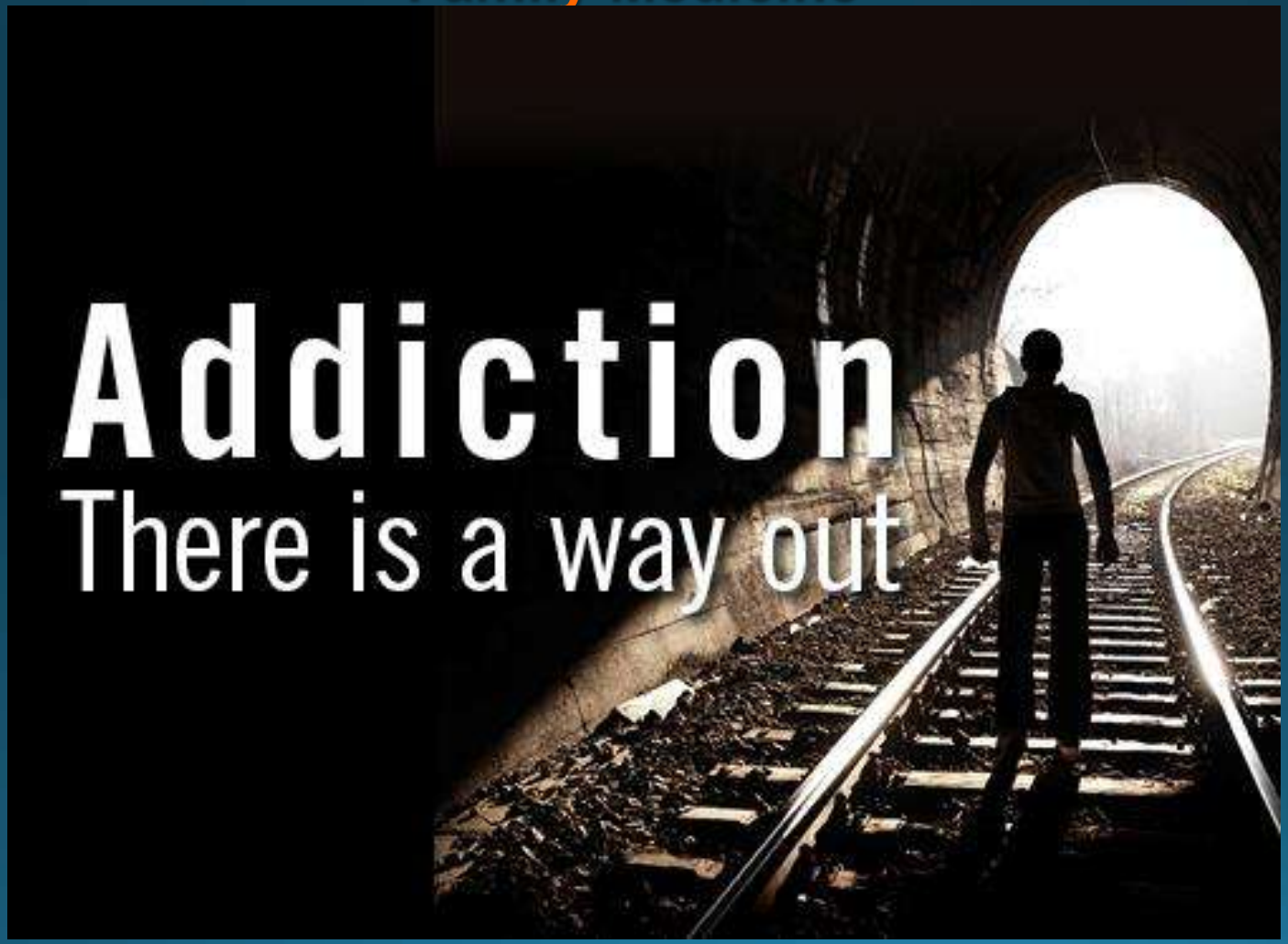
The Neuroscience of Addiction

Darren Caparaso, M.D.
Family Medicine



ASAM Definition of Addiction

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.

Part 1

ASAM Definition of Addiction

Addiction is characterized by inability to consistently abstain, impairment in behavioral control, craving, diminished recognition of significant problems with one's behaviors and interpersonal relationships, and a dysfunctional emotional response. Like other chronic diseases, addiction often involves cycles of relapse and remission. Without treatment or engagement in recovery activities, addiction is progressive and can result in disability or premature death.

Part 2

CHAPTER 2

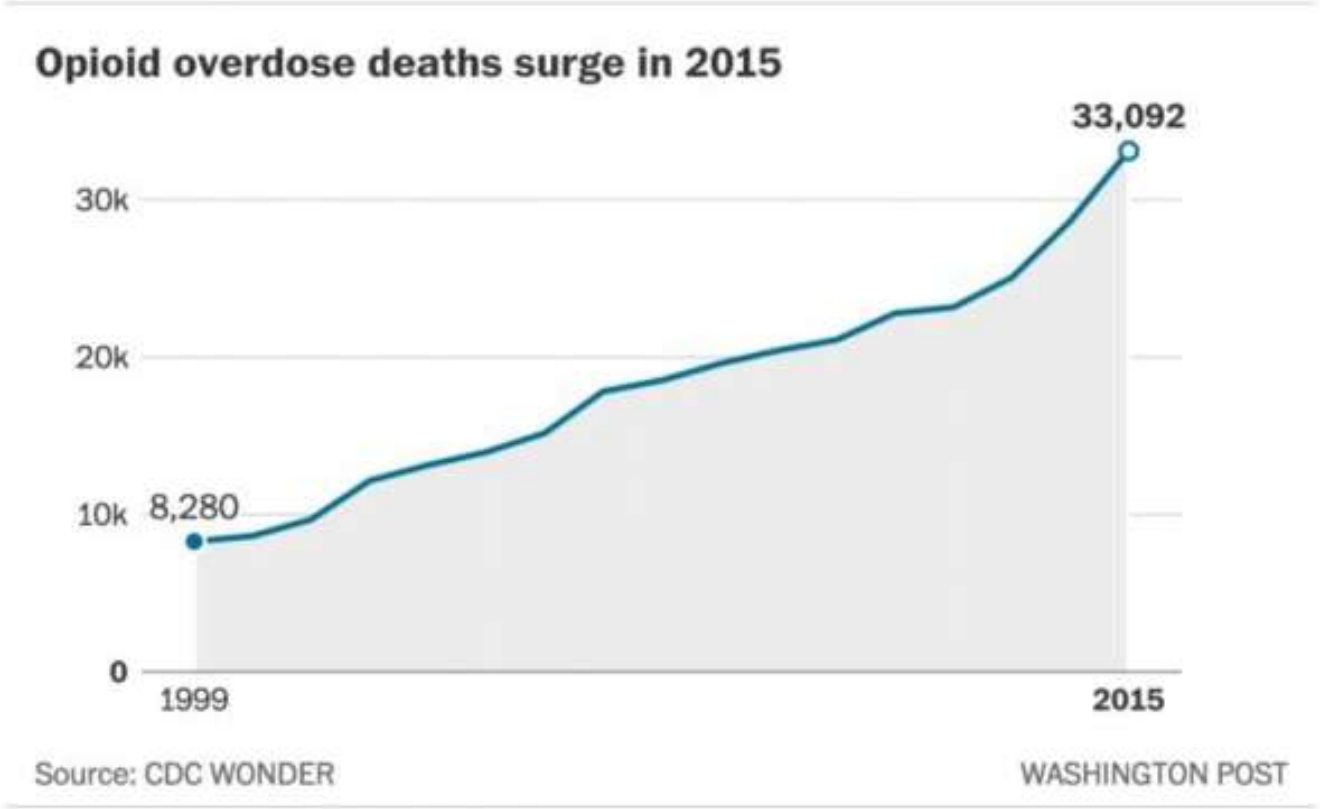
WHY ARE WE HERE?


THE NEW
OLD FACE
OF HEROIN

Papaver Somniferum
"Opium Poppy"

Lethal amounts of Heroin, Fentanyl, and Carfentanil compared

Source: New Hampshire Public Radio/ New Hampshire State Police



WONDER = Wide-ranging Online Data for Epidemiologic Research

Washington Post, 12/8/2016

Erie County Opiate Epidemiic Task Force: Family & Consumer Support and Advocacy Section

Erie County Department of Health

Public Health
Prevent. Promote. Protect.

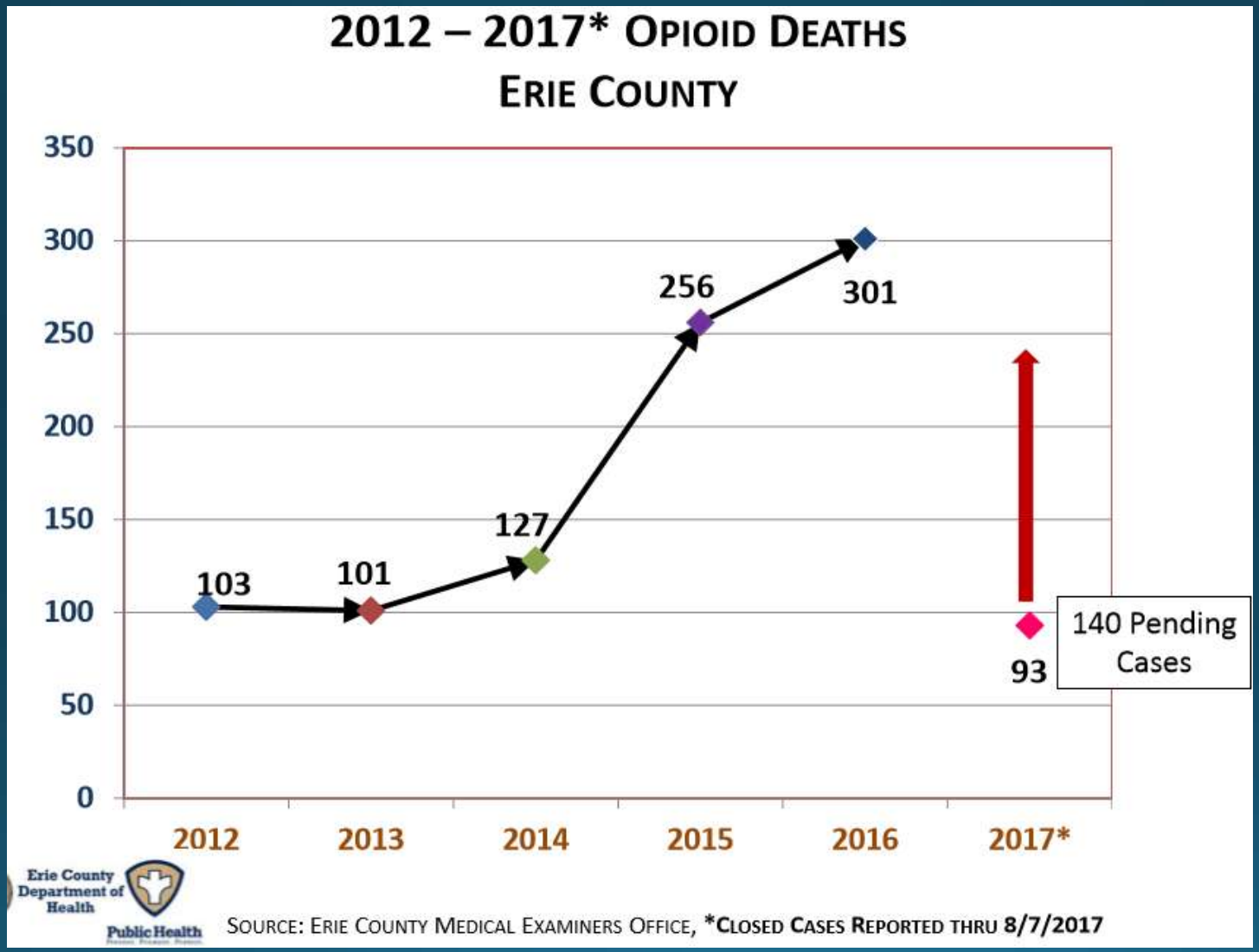
Rapid Evaluation & Appropriate Placement (REAP)	Family & Consumer, Support Advocacy Section	Heroin Opiate Prevention Engagement Project (HOPE)	Provider Education & Policy Reform	Hospitals & Emergency Departments	Naloxone Access	Treatment Providers
Daniel J. Rinaldo NYNJ High Intensity Drug Trafficking Area (HIDTA)	Debra Smith Parent	Barbara Burns Public Affairs Officer US Attorney's Office Western Region of NY	Dr. Gale Burstein Erie County Commissioner of Health & Dr. Paul Updike Medical Director STAR Program Catholic Health	Elizabeth Franzek, MD Attending Physician, VA WNY Healthcare System, Emergency Department	Cheryll Moore Medical Care Administrator Erie County Department of Health	Michael Ranney Erie County Commissioner Of Mental Health

Crossfunctional Collaboration throughout Continuum

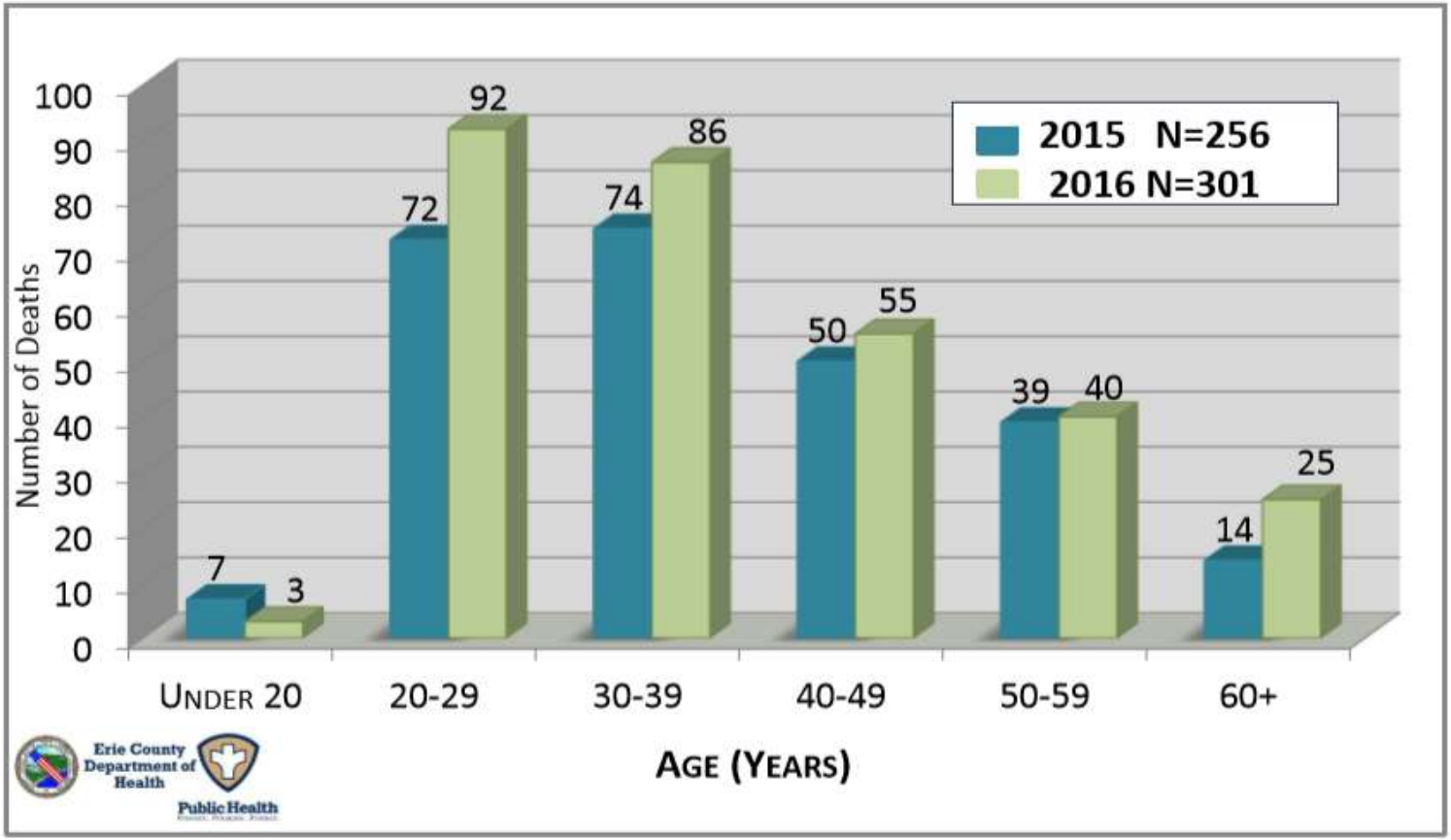
Task Force Mission:

To provide a framework for organizations and individuals from across the opiate overdose continuum to collaborate, develop, and share best practices through timely sharing of information to assist individuals and their loved ones fighting the disease of addiction and to undertake prevention efforts that educate the community on the dangers of addiction.

Revised 9/15/2017


2012 – 2017* Opioid Deaths
Erie County
350
300
250
200
150
100
50
0
103
101
127
256
301
93
140 Pending Cases
2012
2013
2014
2015
2016
2017*
Erie County Department of Health
Public Health
Source: Erie County Medical Examiners Office, *Closed Cases Reported thru 8/7/2017

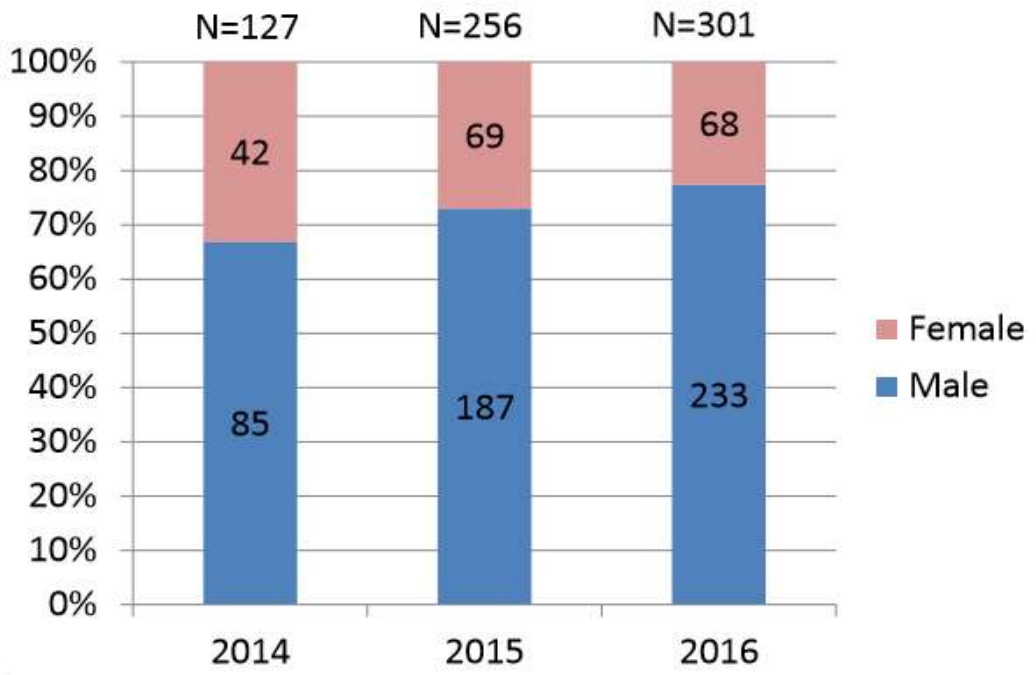
2015 and 2016 Erie County Opioid Deaths by Age and Year



Source: Erie County Medical Examiners Office, **Closed Cases Reported thru 8/7/2017**

2014 – 2016 Erie County Opioid Deaths

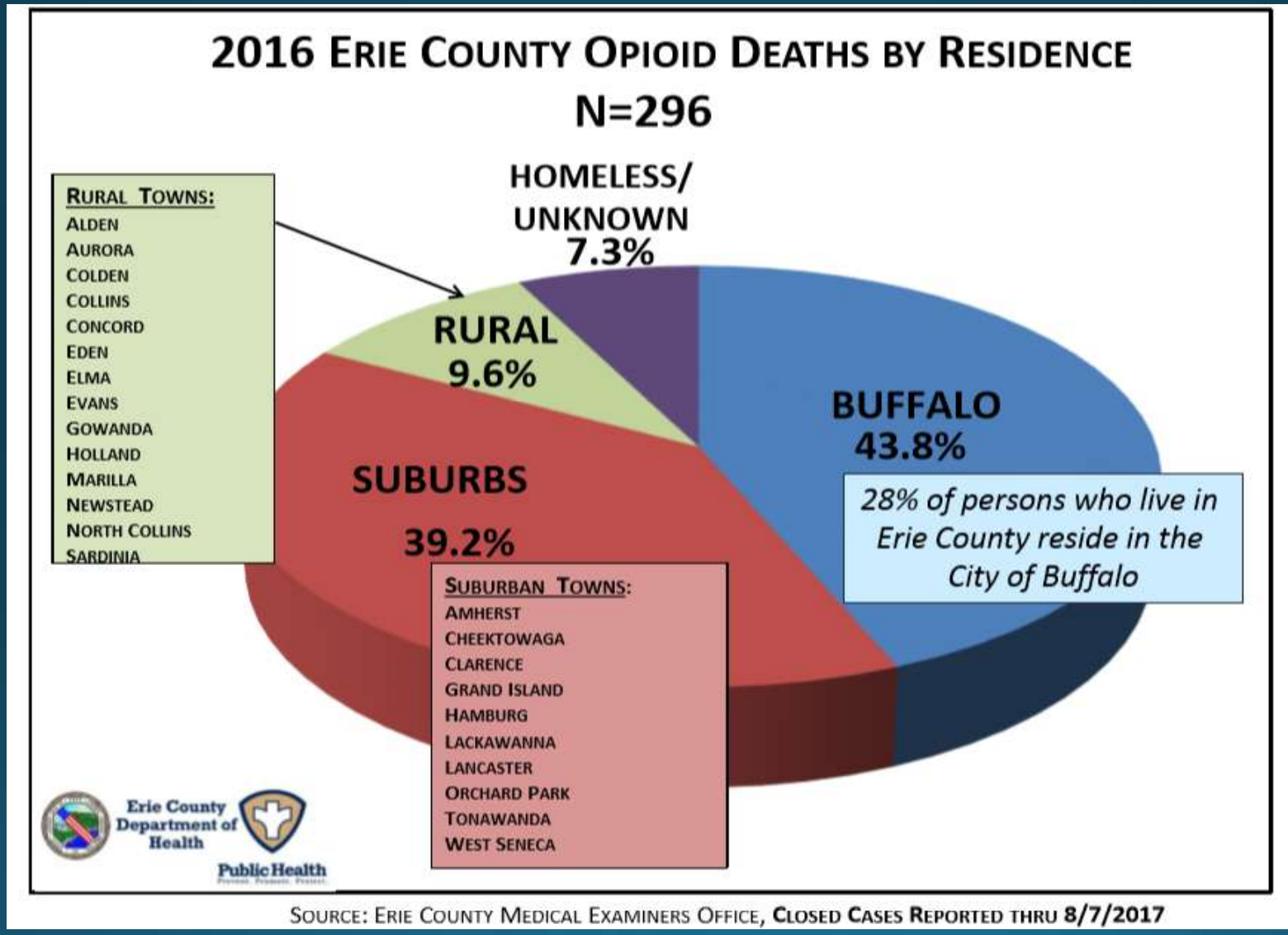
by Gender



Erie County Department of Health

Public Health

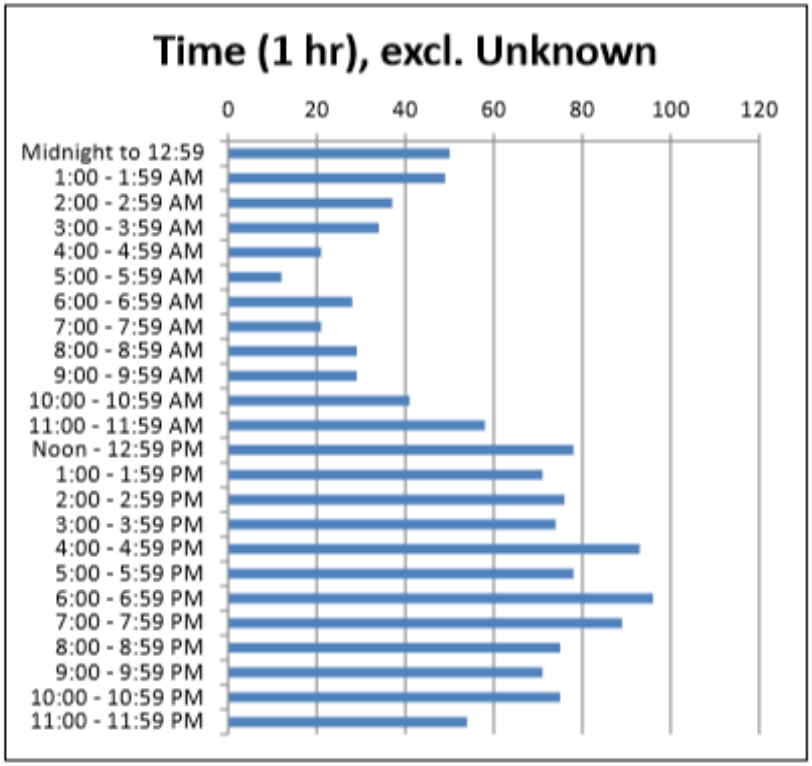
Source: Erie County Medical Examiners Office, **Closed Cases Reported thru 8/7/2017**



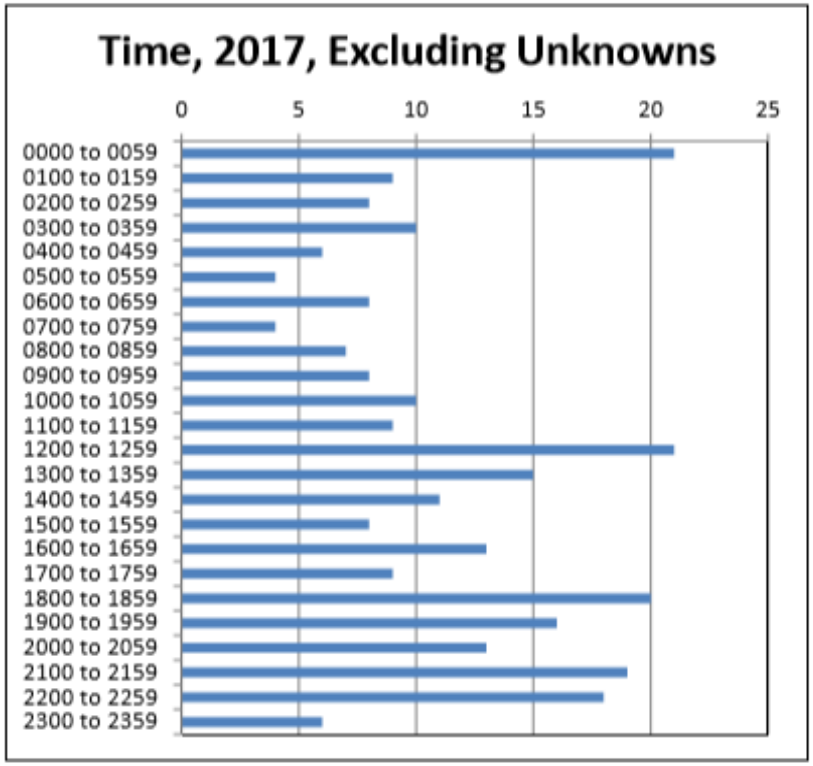
Source: Erie County Medical Examiners Office, **Closed Cases Reported thru 8/7/2017**

Time of Day

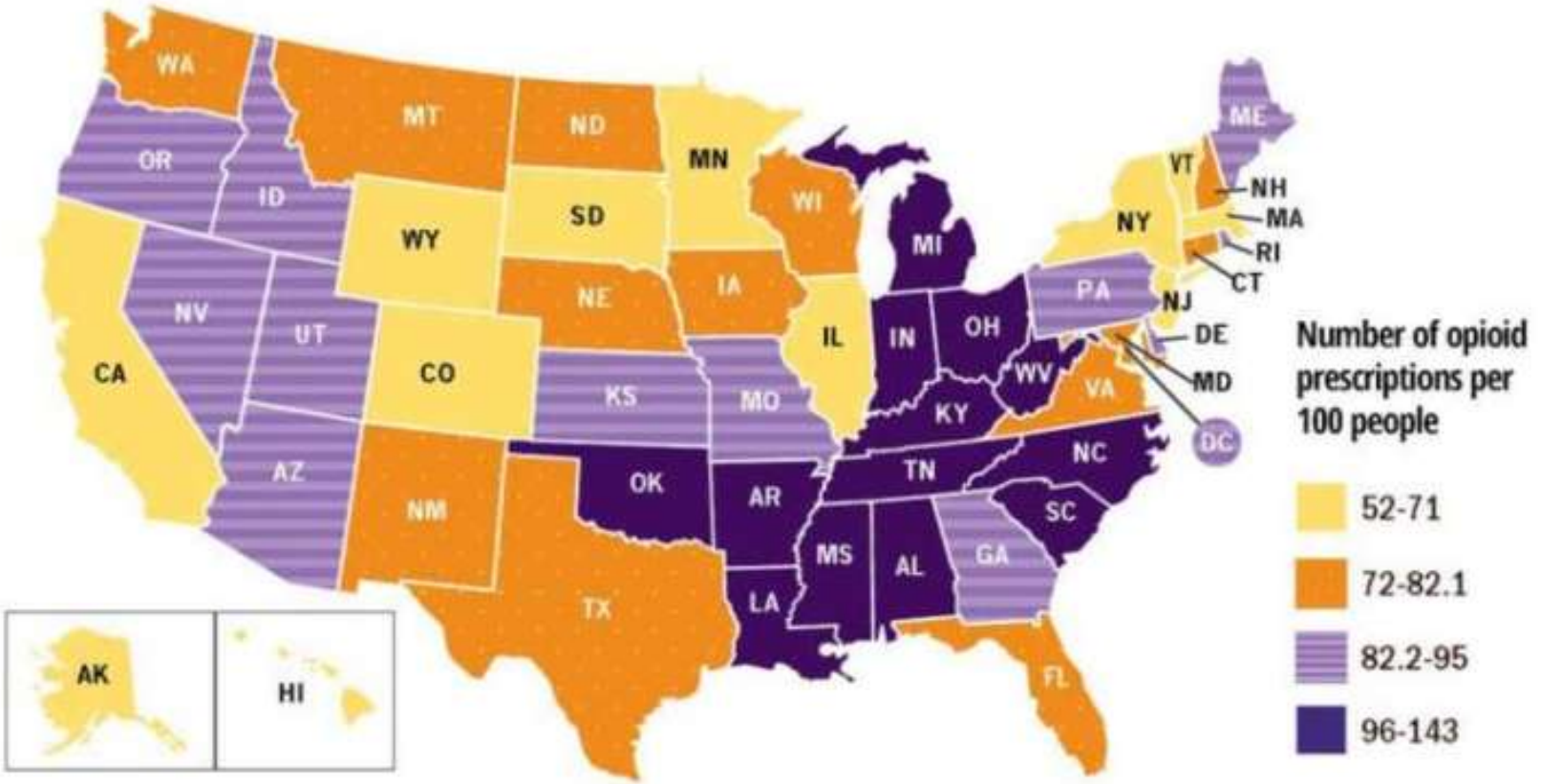
2014 Onwards



2017 So Far



PRESCRIBING PATTERNS



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

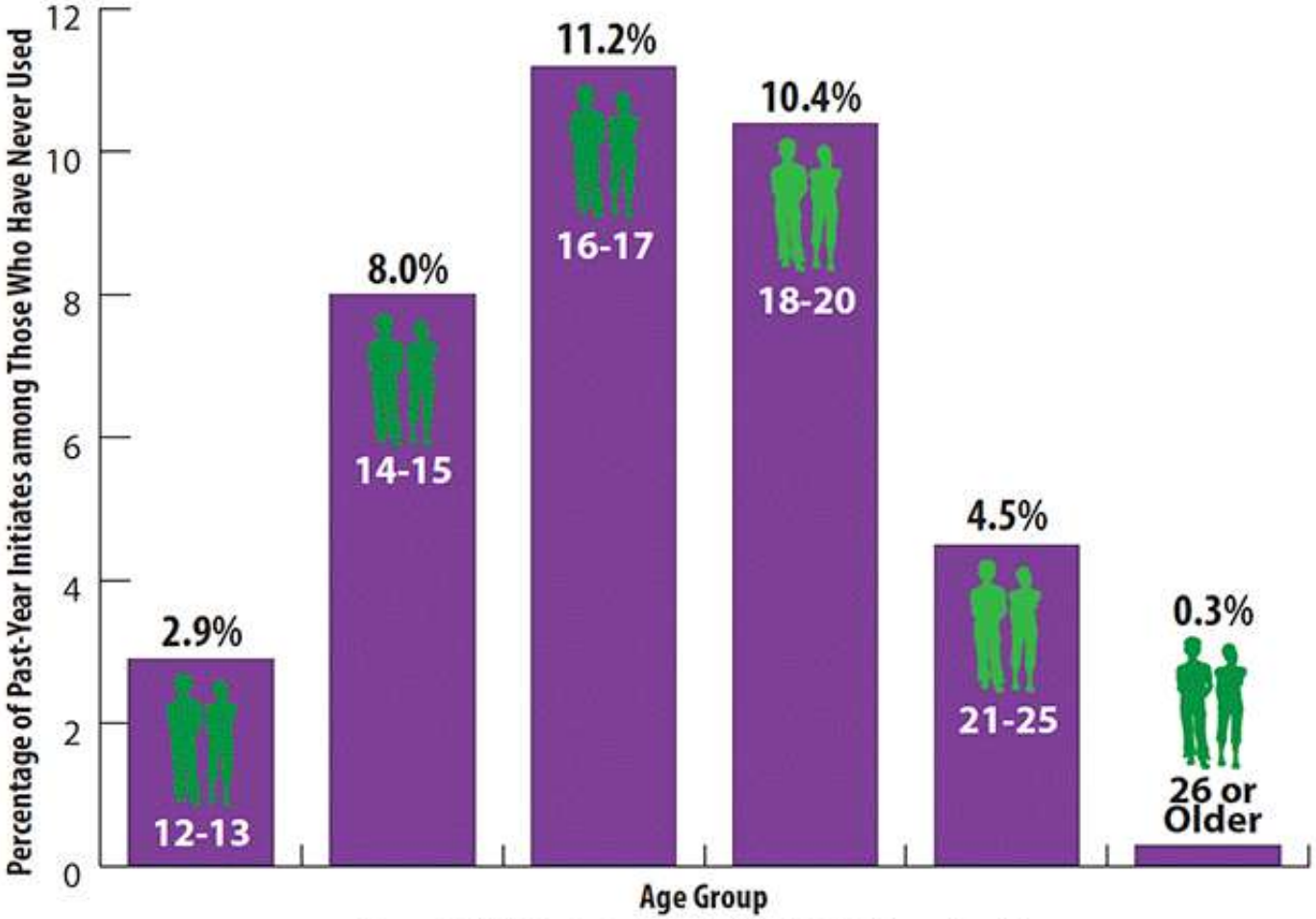
SOURCE: https://www.cdc.gov/drugoverdose/data/prescribing.html

Vulnerability to Addiction

- Several factors contribute to vulnerability:

1. Genetic – both the core DNA and also gene promoters that "turn on" certain genes
2. Early developmental influences and environmental factors
3. Effects of stressful life events across the life cycle
4. Co-occurring mental disorders – principally depression and anxiety

The Drug Danger Zone: Most Illicit Drug Use Starts in the Teenage Years



Source: SAMHSA, Center for Behavioral Health Statistics and Quality, National Survey on Drug Use and Health, 2011 and 2012.

Heroin use is part of a larger substance abuse problem.

Nearly all people who used heroin also used at least 1 other drug.

Most used at least 3 other drugs.

Heroin is a highly addictive opioid drug with a high risk of overdose and **death** for users.

People who are addicted to...

are **2x**

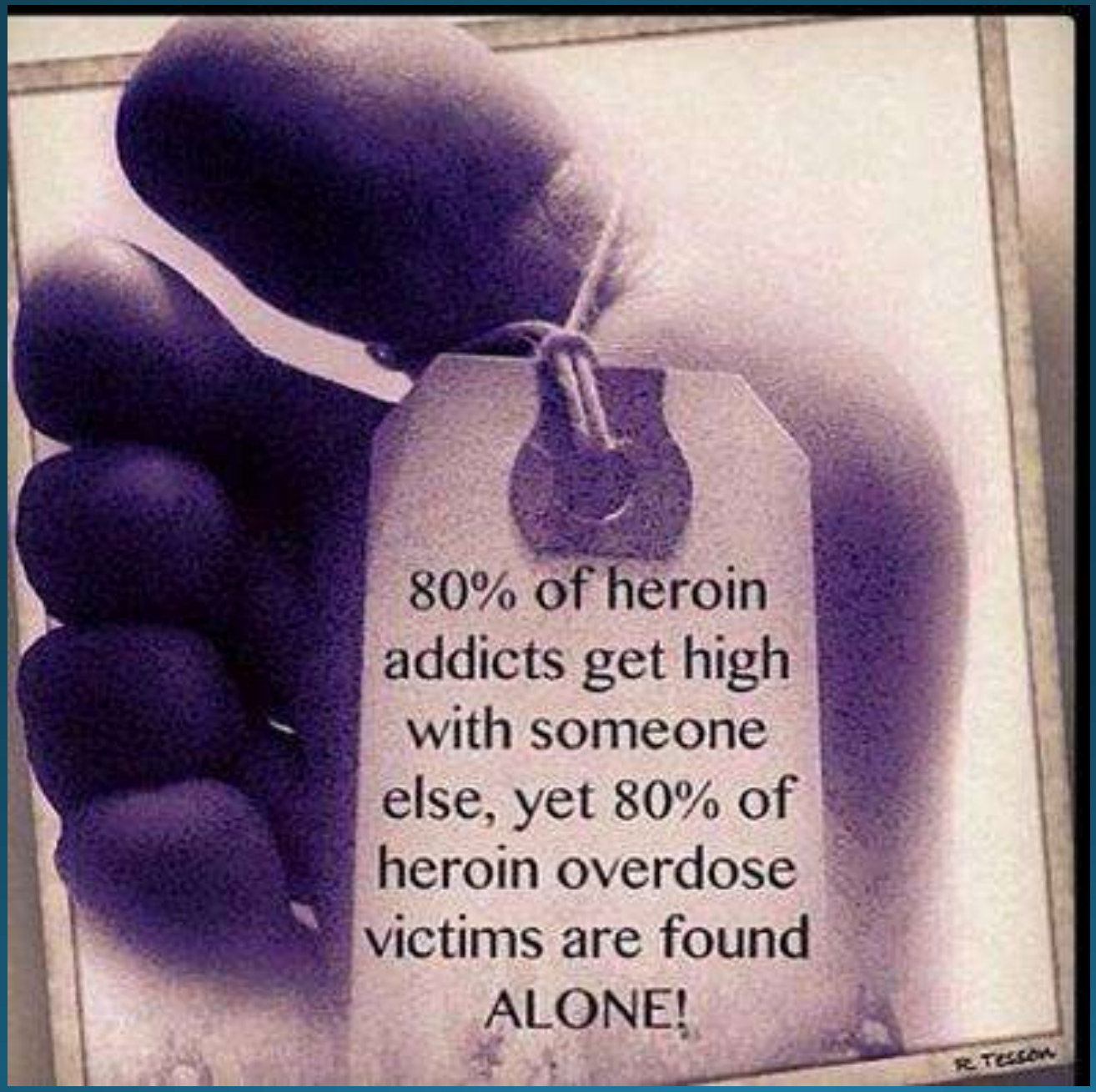
are **3x**

are **15x**

are **40x**

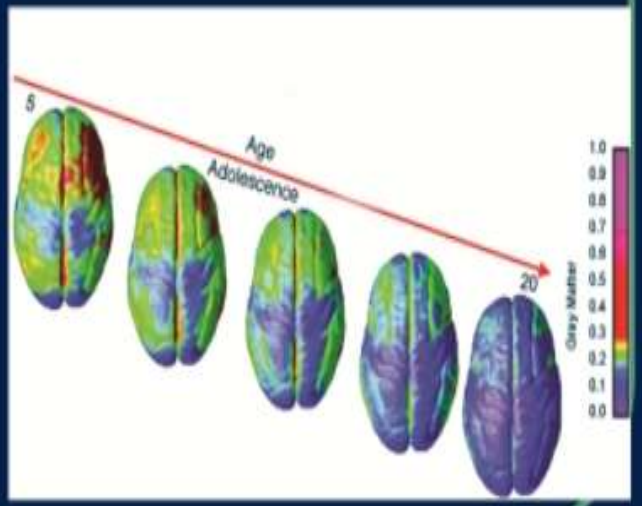
...more likely to be addicted to heroin.

SOURCE: National Survey on Drug Use and Health (NSDUH), 2011-2013.


80% of heroin addicts get high with someone else, yet 80% of heroin overdose victims are found ALONE!
R. TESSON

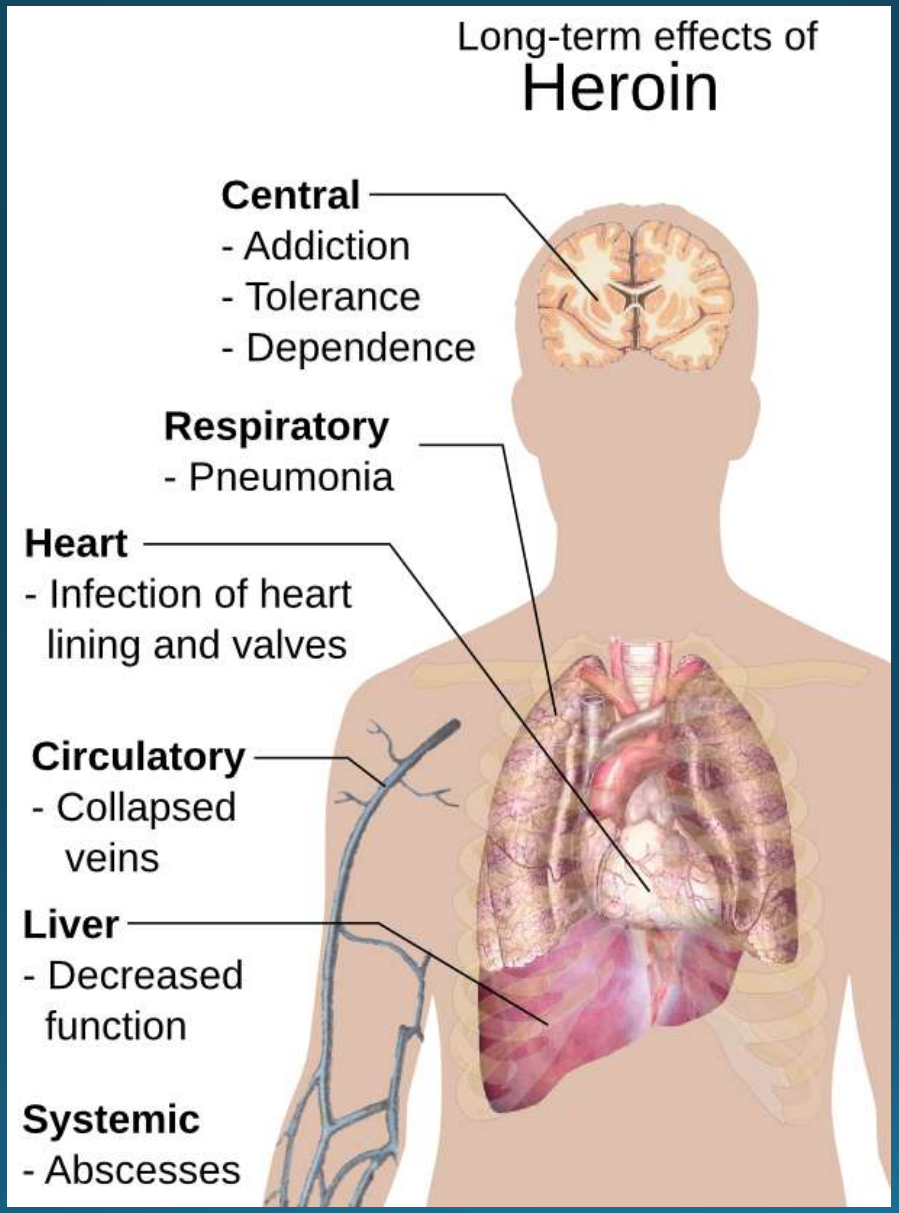
Adolescents Are Vulnerable

- Early substance use = high risk of addiction
- Adolescent immaturity during critical development period = vulnerability
  - Impulsiveness and excitement seeking
  - Difficulty delaying gratification
  - Poor executive function and inhibitory control



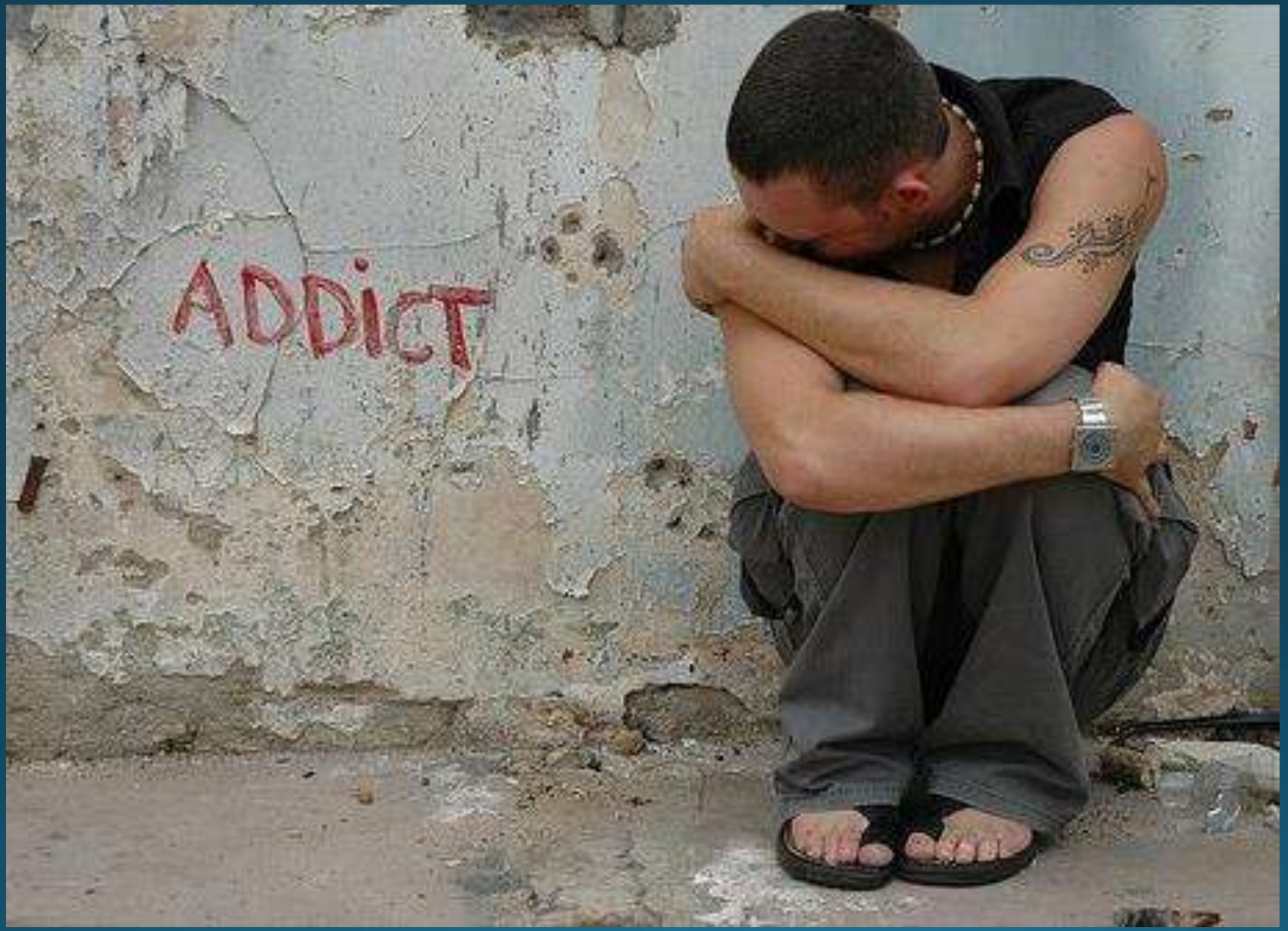
Early Drug Use

- The literature has long held that repeated drug use before age 14 is associated with far greater likelihood of adult addiction.
- The reward centers of the brain, being more primitive, develop before the frontal cortex.
- Thus, with early drug use, the brain gets stimulated intensely but does not yet have the ability to put the frontal lobe brakes on.


Long-term effects of
Heroin
Central
- Addiction
- Tolerance
- Dependence
Respiratory
- Pneumonia
Heart
- Infection of heart lining and valves
Circulatory
- Collapsed veins
Liver
- Decreased function
Systemic
- Abscesses

Genetics

- Evidence has been found for a genetic influence on alcoholism, opiate dependence and, less robustly, other CNS depressants such as tranquilizers.
- Genes do not make the disorder; they merely present an increased vulnerability to having the disorder.
- Genetic vulnerability to depression and anxiety can also contribute to a vulnerability to drug dependence.
- Gene expression can also be altered by life experiences as with chronic severe depression


ADDICT

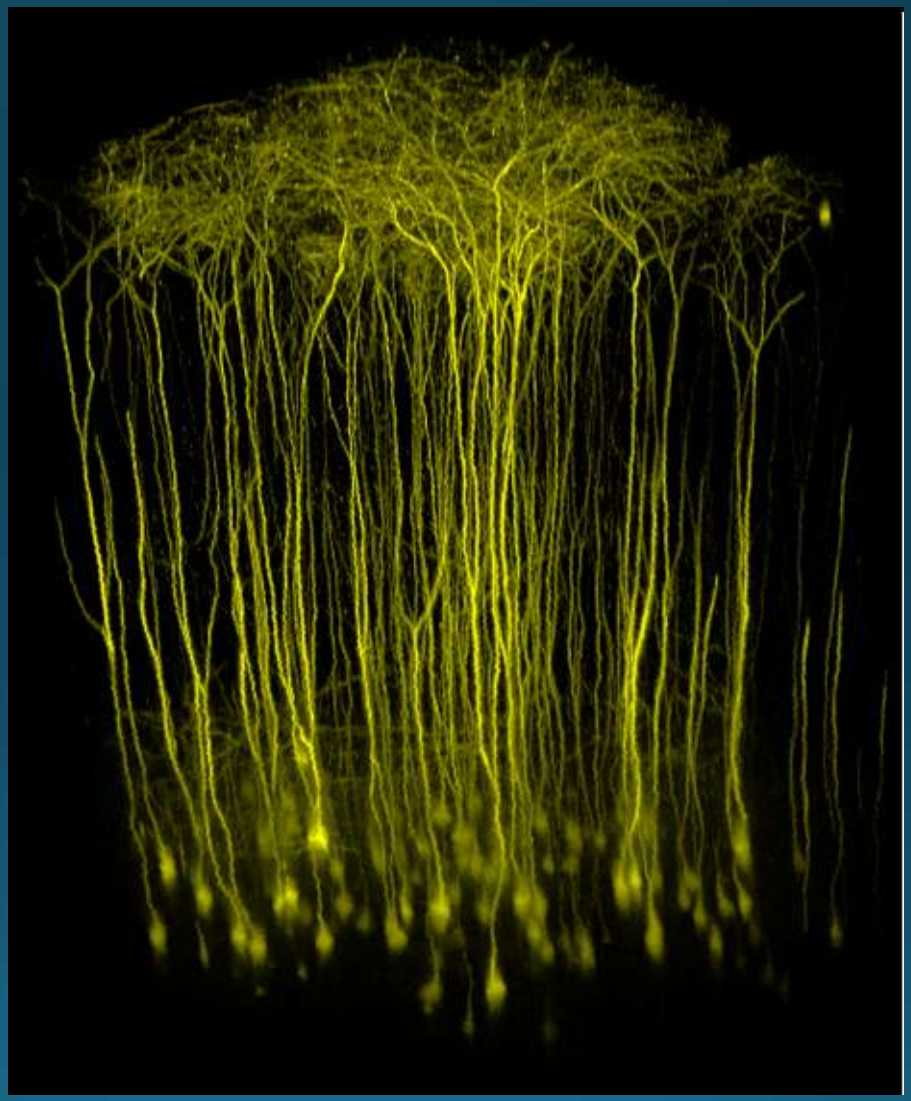
Brain and Behavior: The 2-Way Street

- Thinking, feeling and behaving *are produced* by brain anatomy and chemistry.

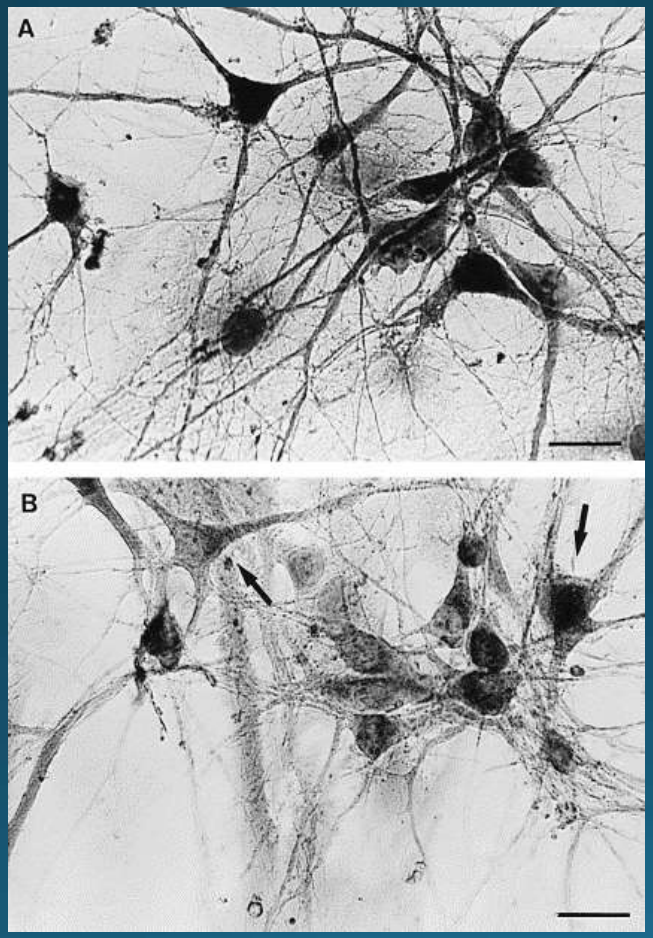
- Conversely, thinking, feeling and behaving *shape* the development of brain anatomy and chemistry.

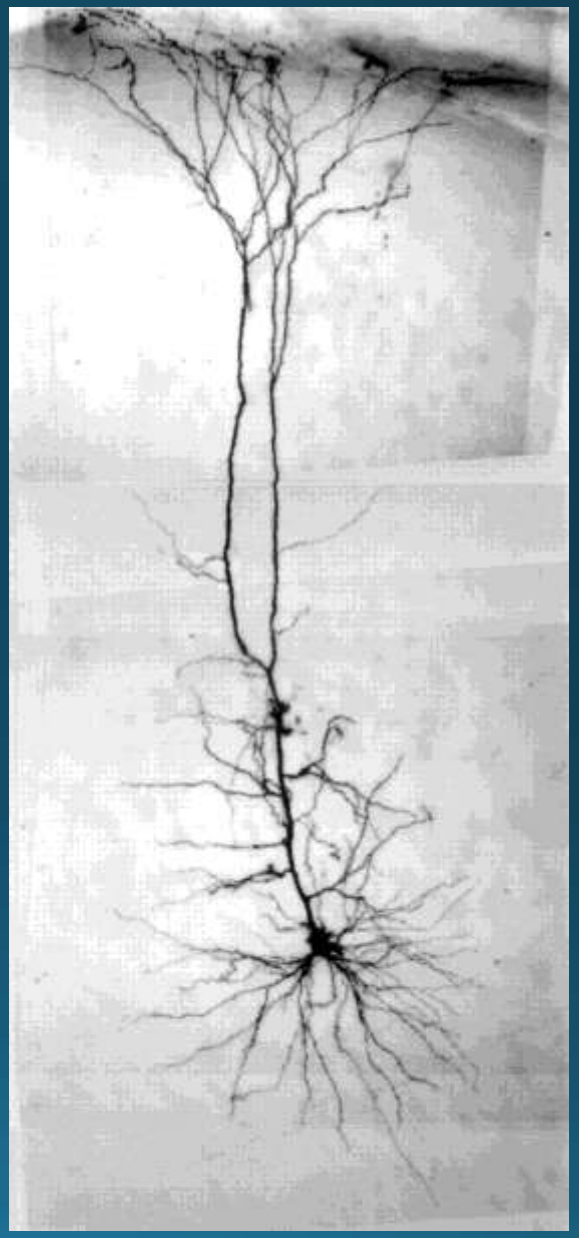
Time for anatomy
Let's start small

Each neuron with 6,000-10,000 connections to other cells. These are pyramidal cells in the cortex, radiating in toward the white matter regions.



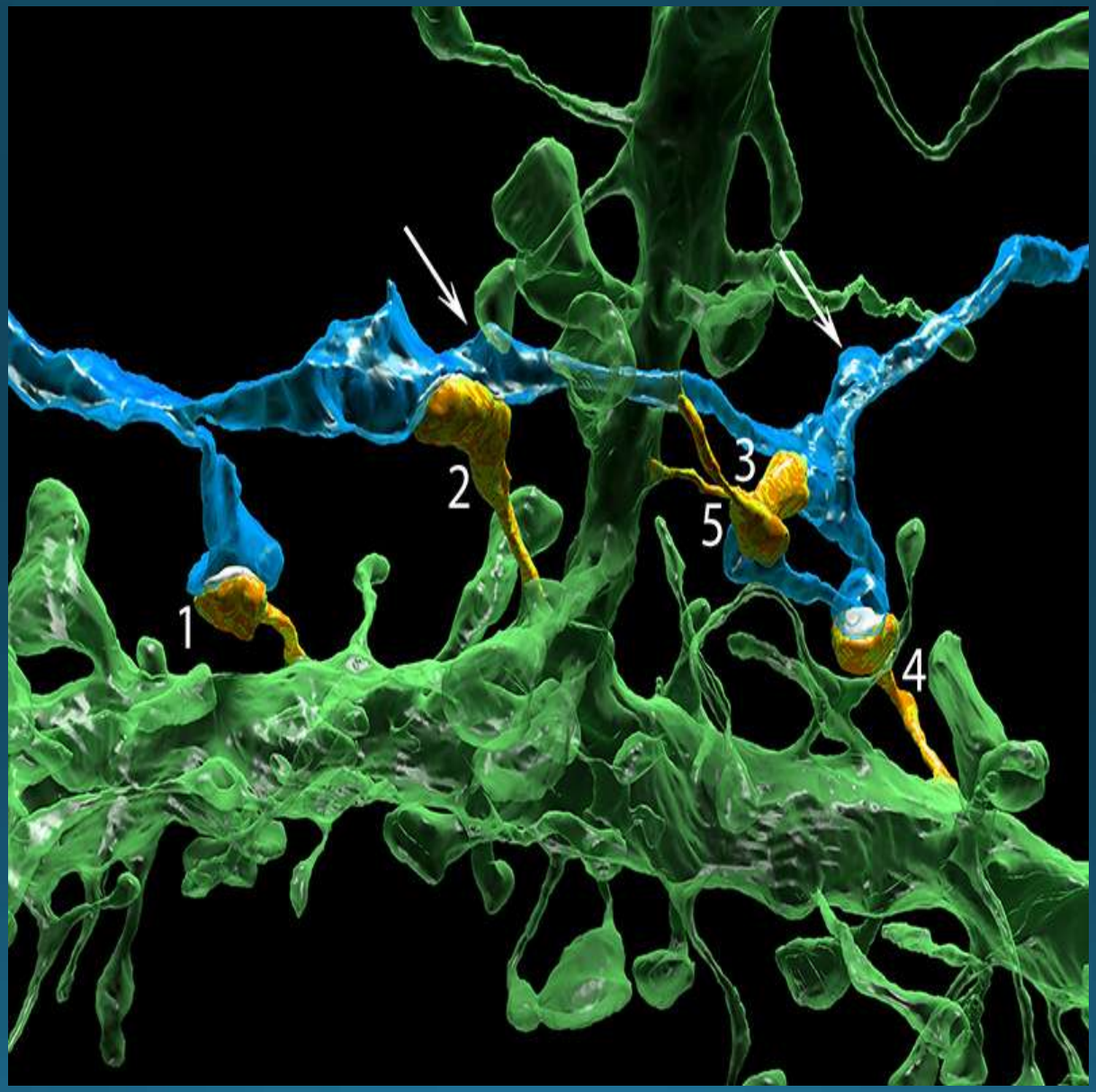
What they actually look like





http://www.sciencedirect.com/science?_

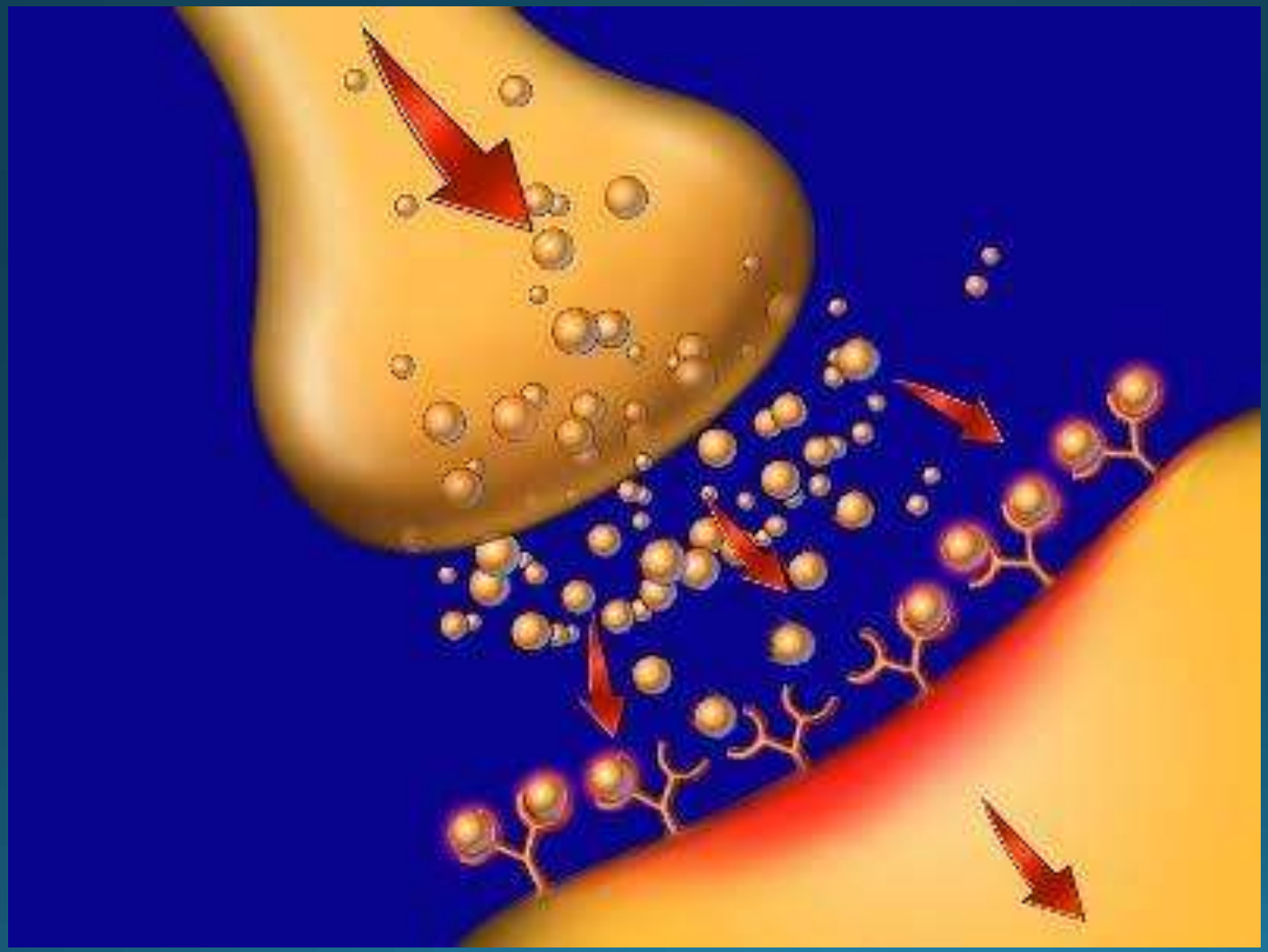
Two neurons – one green, one blue – synaptic connection regions in yellow. The bulbs are called spines and they are the beginning points of receptivity. Some will become dendrites.

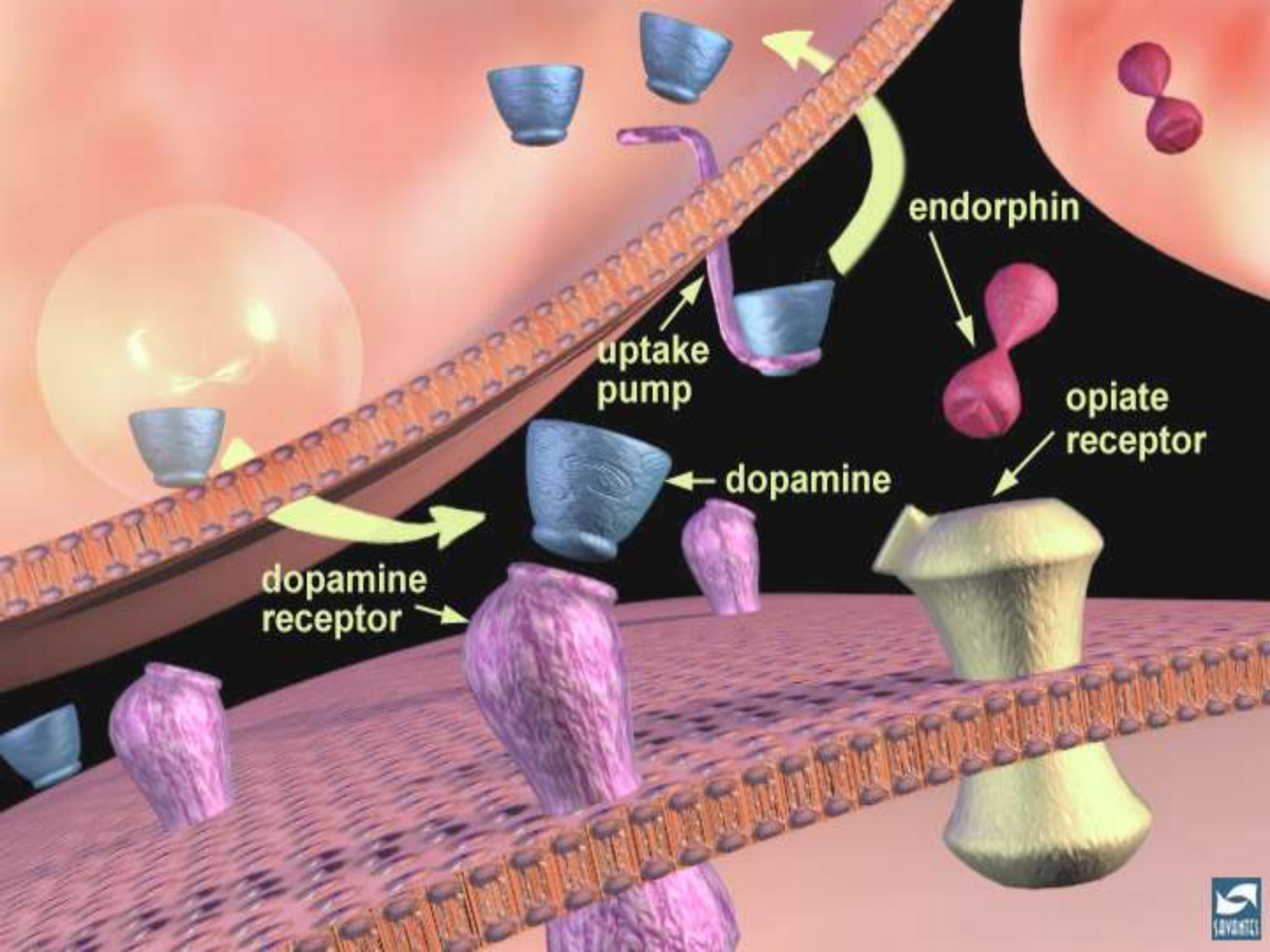


Neurotransmitters

- Neurons communicate across synaptic gaps by discharging and absorbing neurotransmitters.
- Neurotransmitters are complex organic messenger molecules.
- There is scientific data on about 50 neurotransmitters and there are probably some 300 neurotransmitters in the human brain.
- The production and absorption of neurotransmitters is basically set by genetic codes and both production and absorption can be altered by drug use, diseases, environmental exposures, and life experiences.

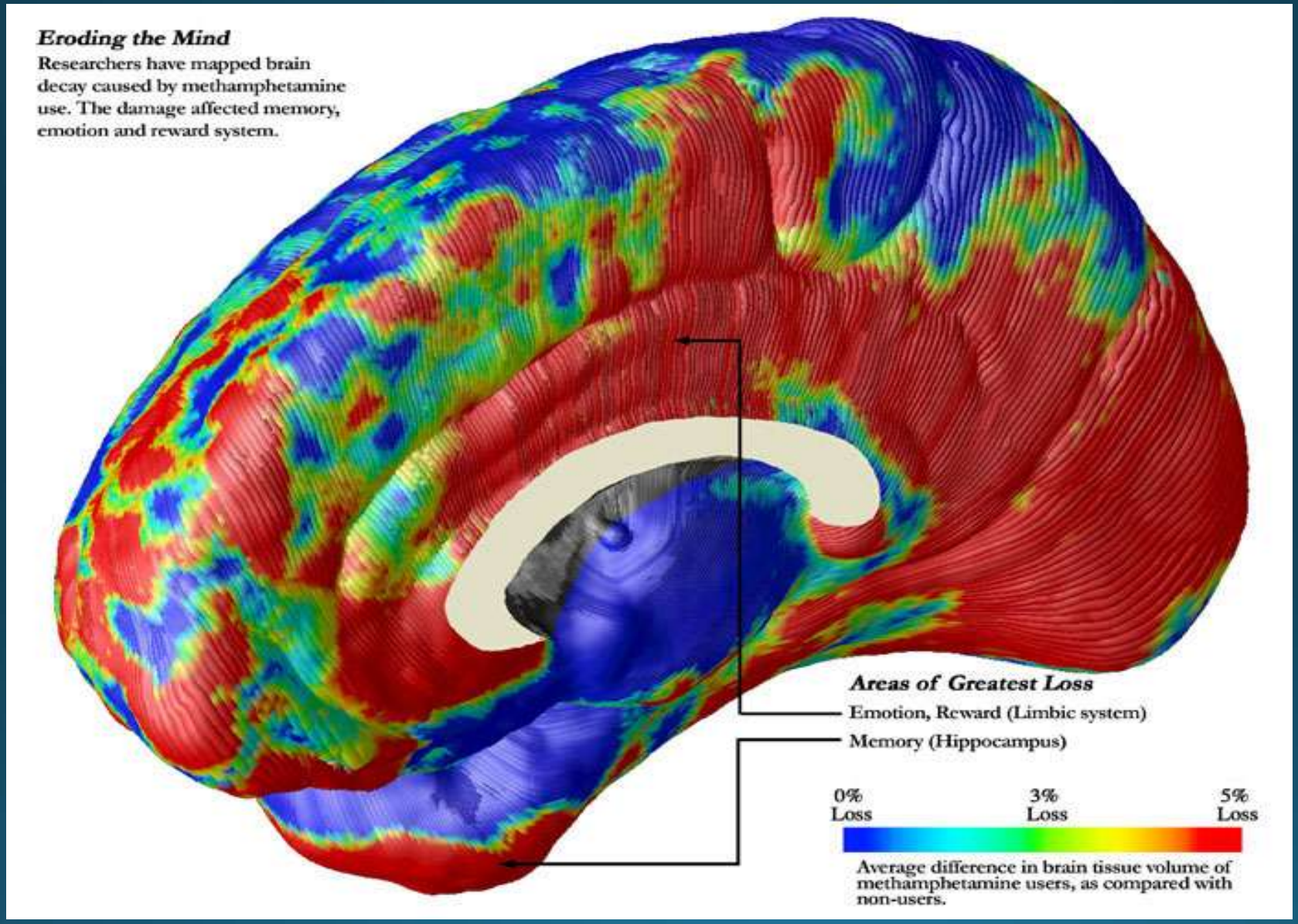
Nerves talking




endorphin
uptake
pump
opiate
receptor
dopamine
dopamine
receptor

Memory and its structures

- All memoral functions have neurochemical and neuroanatomical correlates.
- Memory is widely distributed throughout the brain BUT all memory is mapped into neural pathways at specific regions of the brain.
- Addiction experiences are deeply involved with memory systems and also change those systems.
- We remember only that which has emotional valence.


Eroding the Mind
Researchers have mapped brain decay caused by methamphetamine use. The damage affected memory, emotion and reward system.
Areas of Greatest Loss
Emotion, Reward (Limbic system)
Memory (Hippocampus)
0% Loss
3% Loss
5% Loss
Average difference in brain tissue volume of methamphetamine users, as compared with non-users.

WHAT IS THE HIPPOCAMPUS?

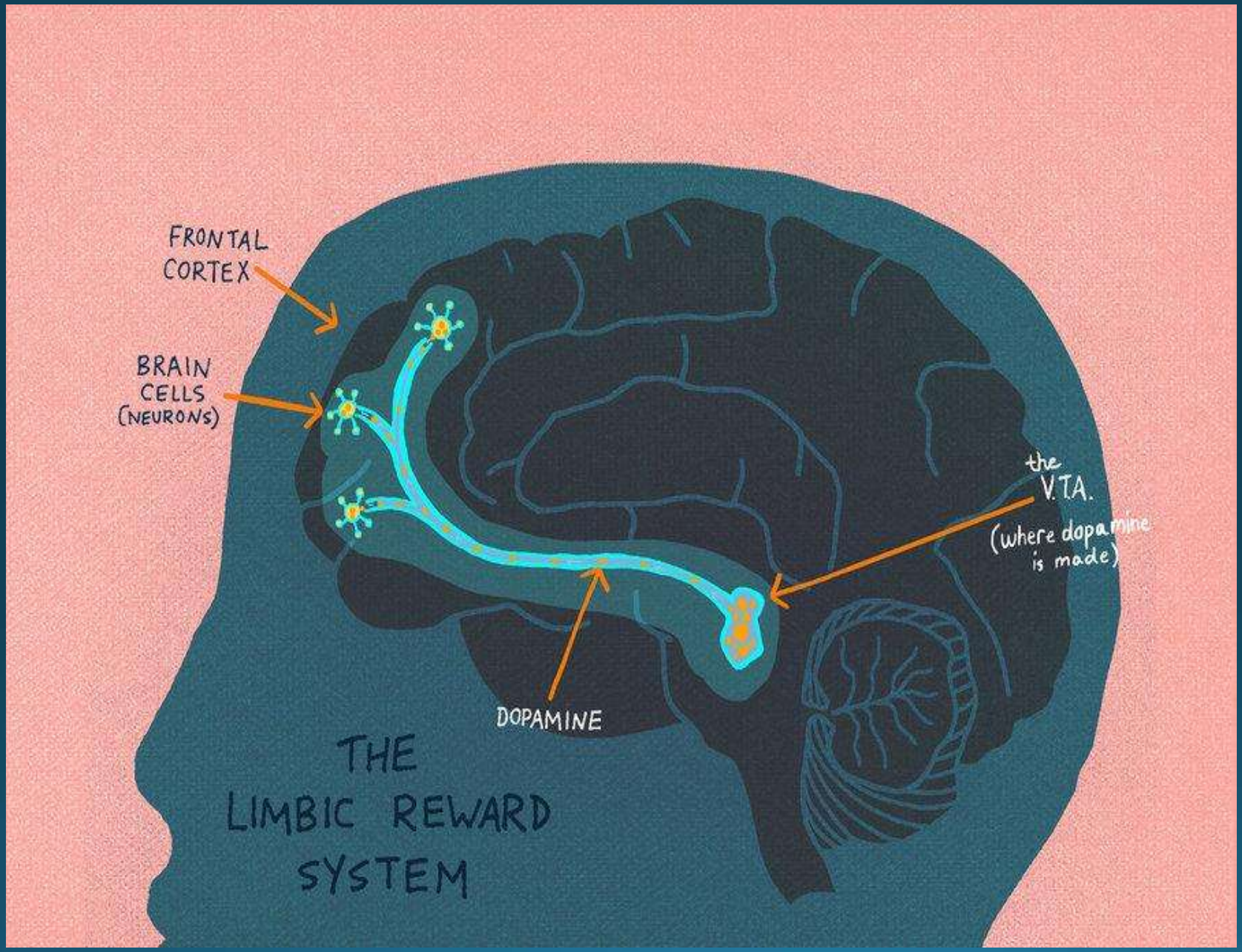
- The hippocampus also plays a role in retrieval of memories.

- It is sensitive to negative effects of cortisol and research has found decreased cell volume in the hippocampi of individuals with:
  - PTSD
  - Depression
  - Alcoholism
  - Chronic, heavy sustained use of marijuana

- The same finding for the amygdala, which is heavily involved with emotional memory – and negative emotional memory in particular.

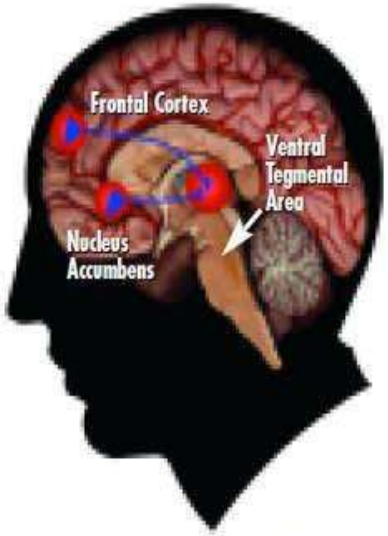
What is the arousal system?

Time to talk Limbic


FRONTAL CORTEX
BRAIN CELLS (NEURONS)
the V.T.A. (where dopamine is made)
DOPAMINE
THE LIMBIC REWARD SYSTEM

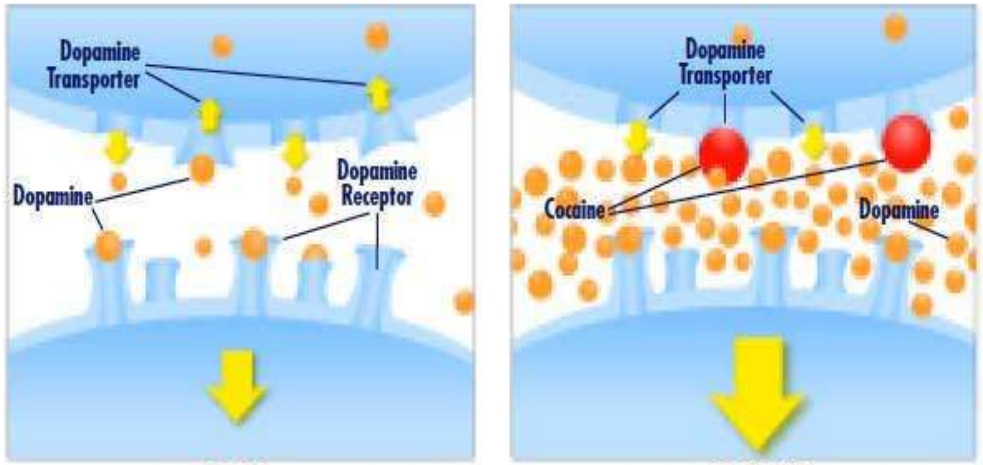
DRUGS OF ABUSE TARGET THE BRAIN'S PLEASURE CENTER

Brain reward (dopamine) pathways



These brain circuits are important for natural rewards such as food, music, and sex.

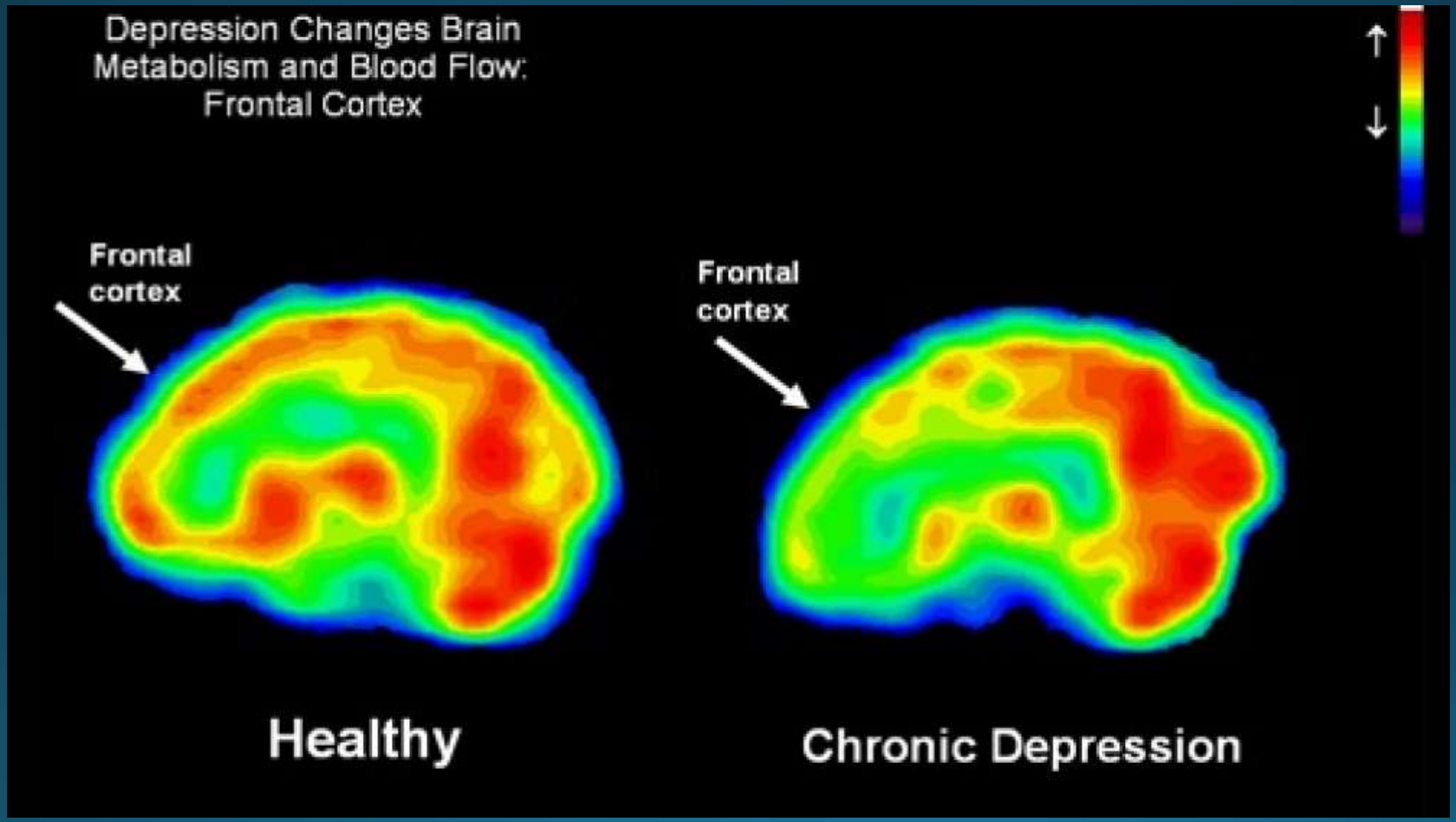
Drugs of abuse increase dopamine



FOOD COCAINE

Typically, dopamine increases in response to natural rewards such as food.
When cocaine is taken, dopamine increases are exaggerated, and communication is altered.

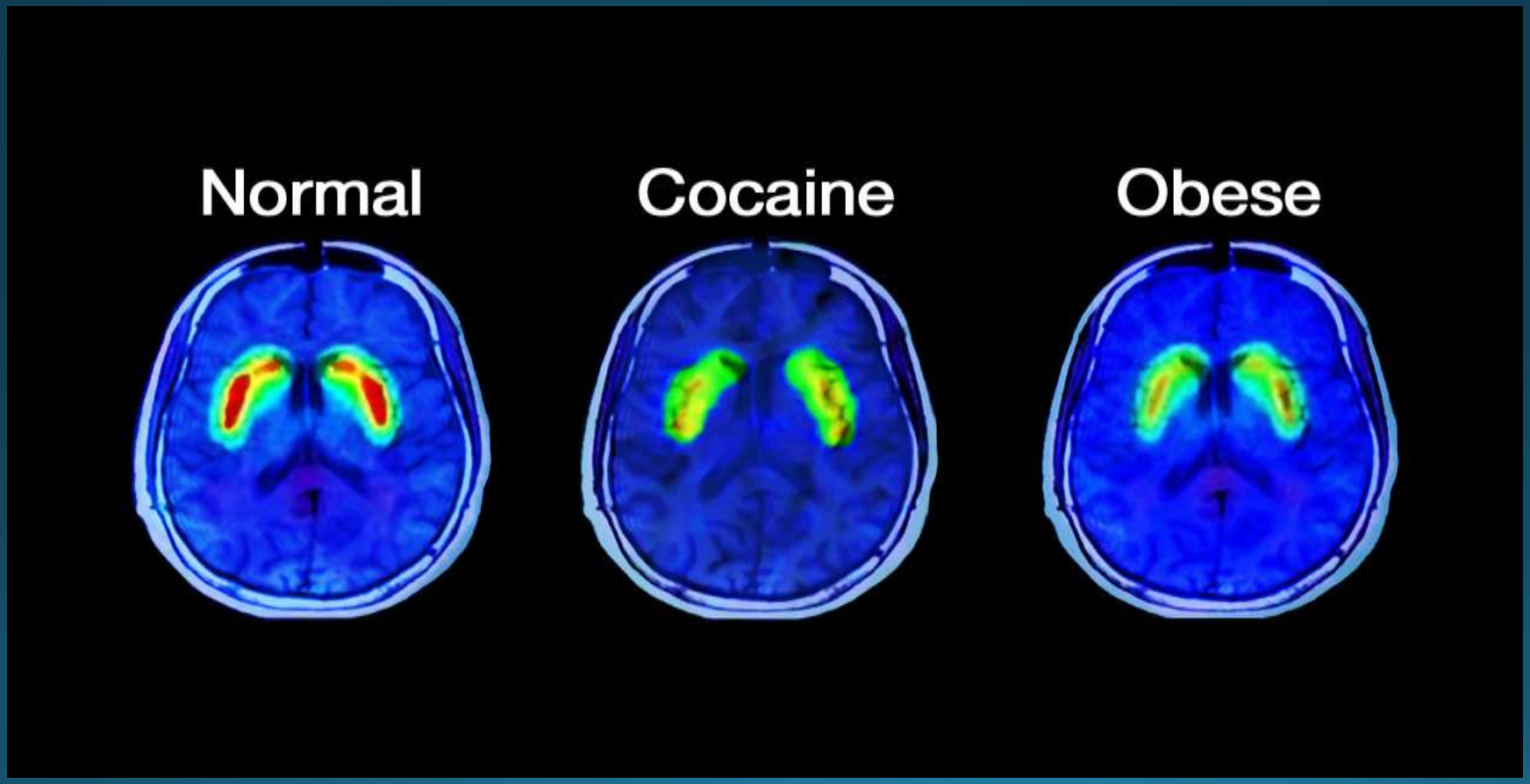
This shows reduced blood flow in the frontal cortex with depression



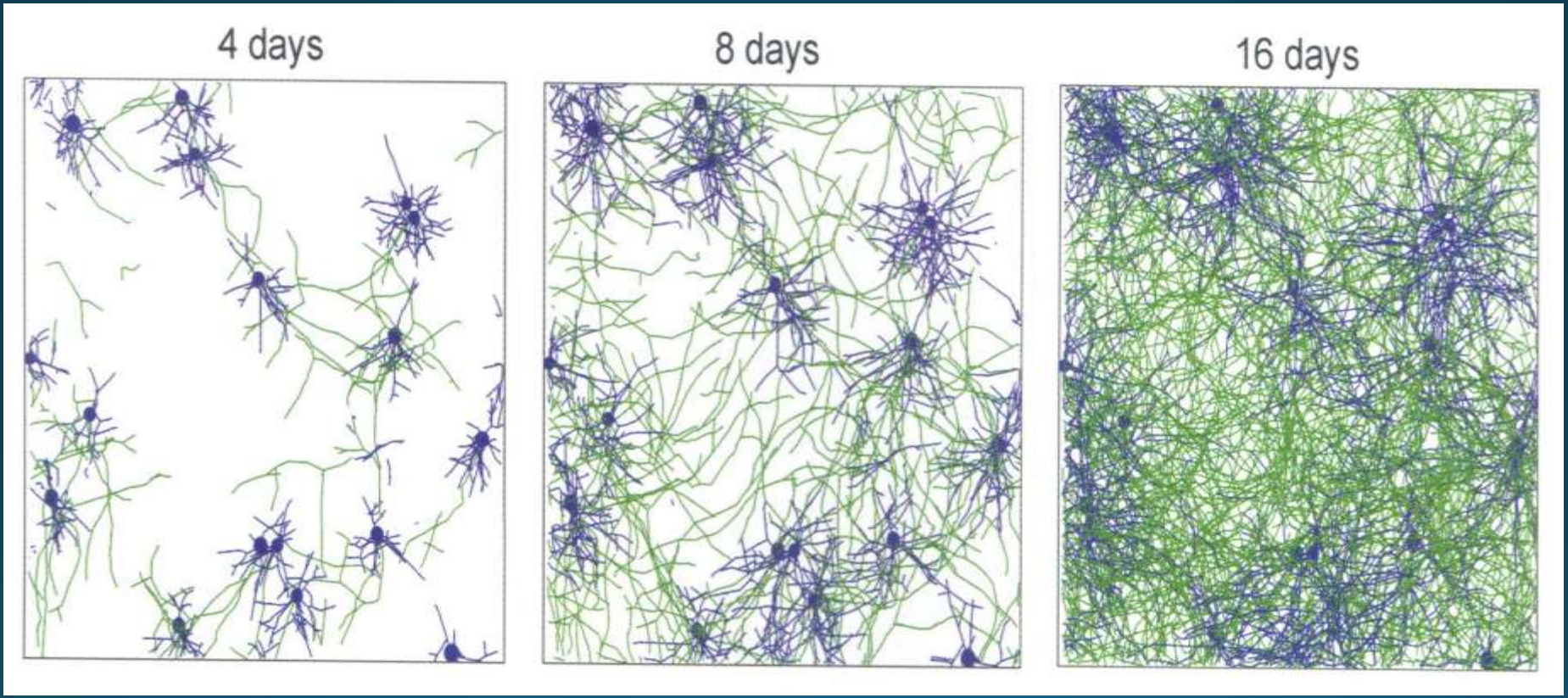
Anxious and Depressed

- Heightened or sustained arousal states are associated with depression.
- About 50% of patients with anxiety disorders also have depression.
- Has correlates with ego depletion.

Blunted reward system from drug use



Neural dendritic growth: synaptogenesis



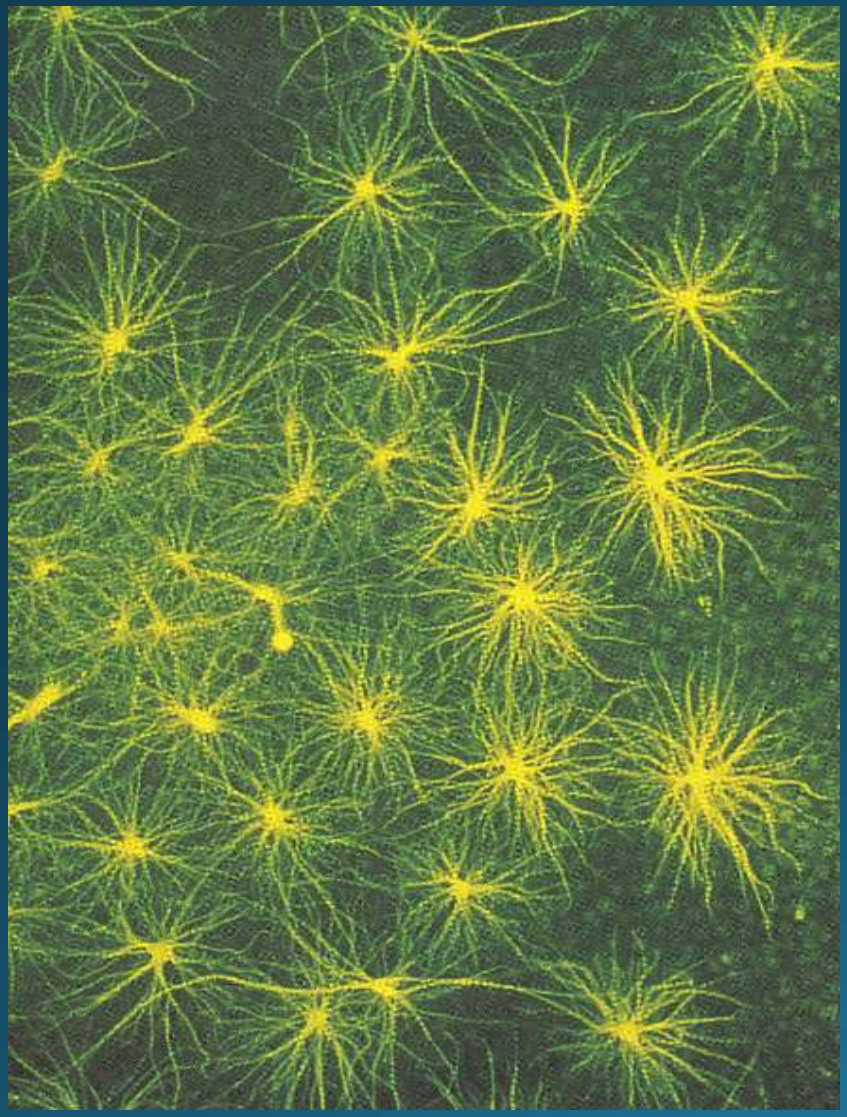
Sporns, O. (2011). Networks of the Brain. Cambridge, MA: MIT Press. Sporns bathed neurons in NMDA (the neurotransmitter than activates long term potentiation memory. One can see the growth of connectivity in a short time.

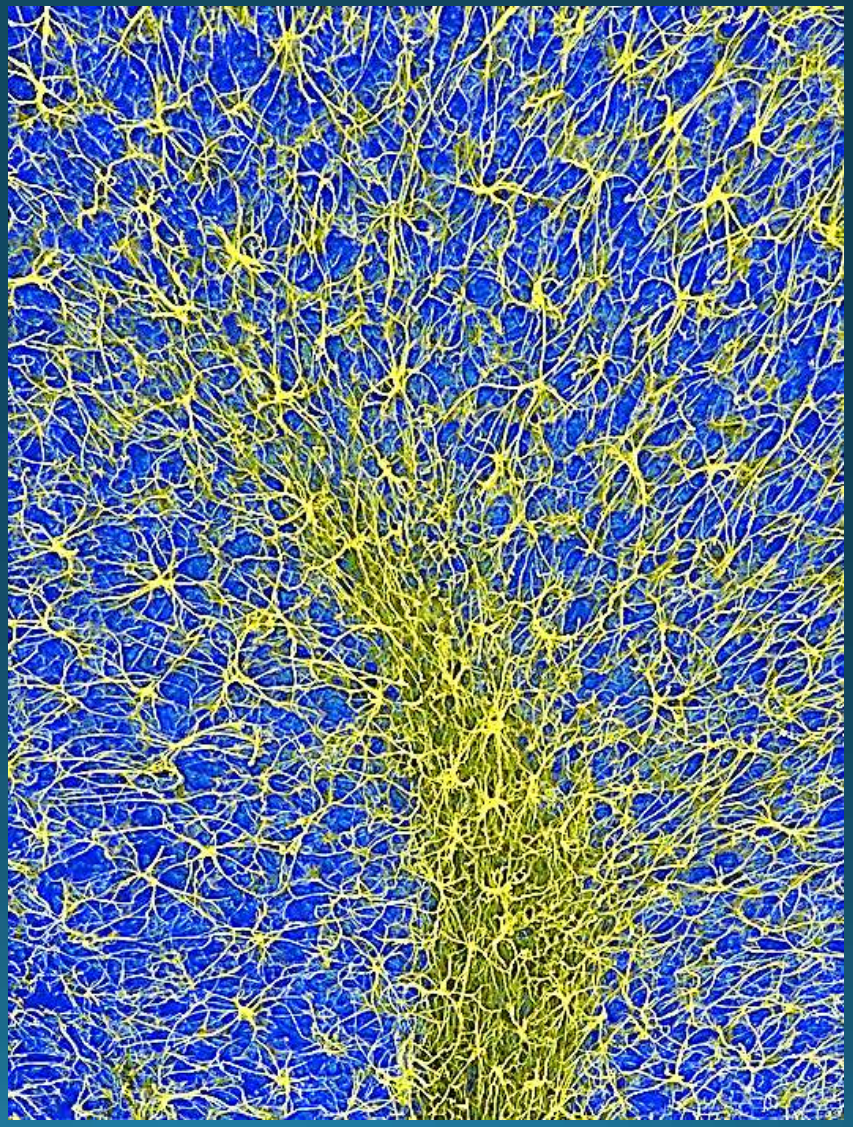
Reward, Pleasure, Memory

- The brain regions responsible for mediating pleasure are located very close to memory centers and other key emotion sensing areas –
  - The hippocampus – memory encoding and retrieving
  - The amygdala – emotion-tagging system

- They are also closely related to centers that mediate intentional actions.
  - Striatum

Astrocytes



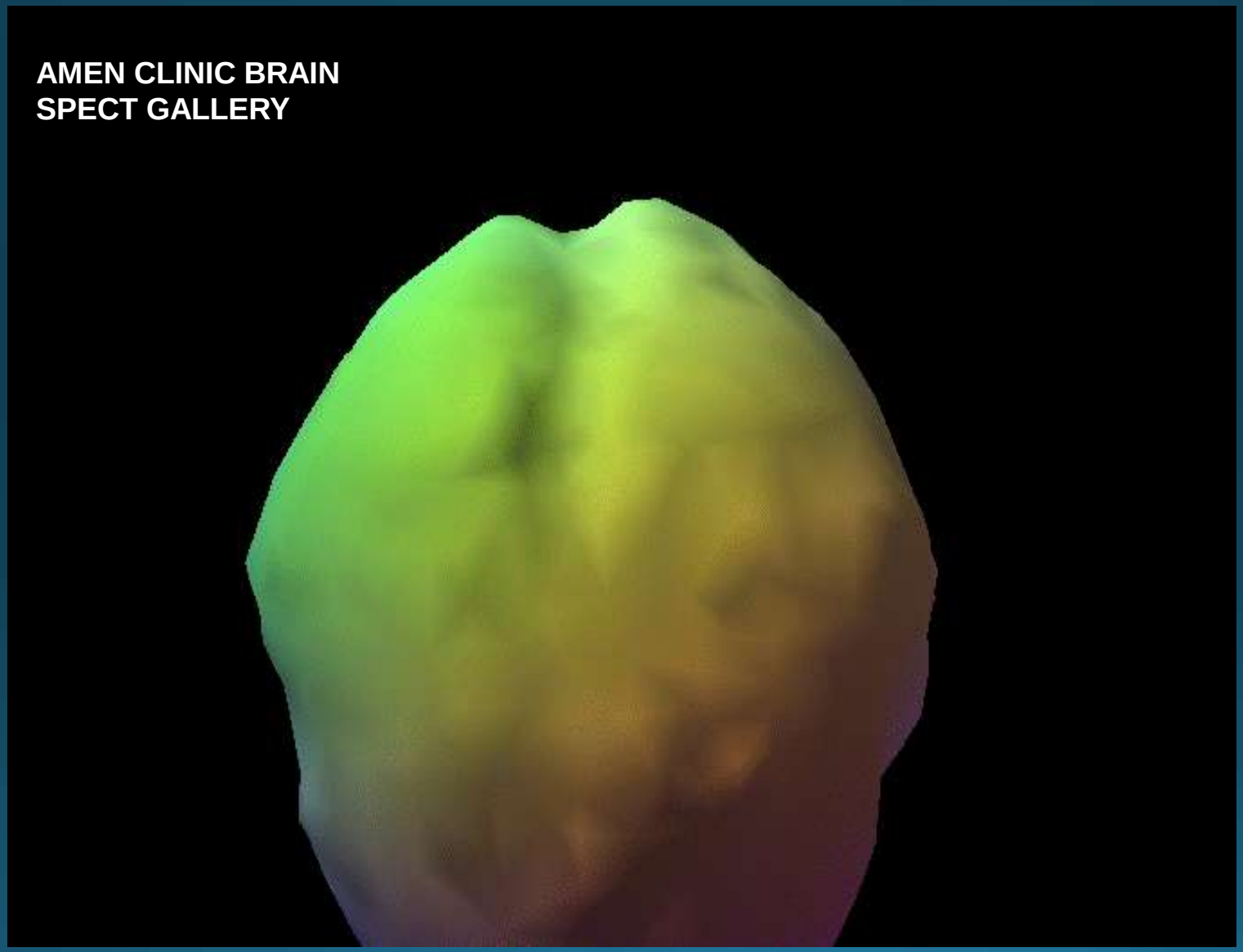


Brain Power

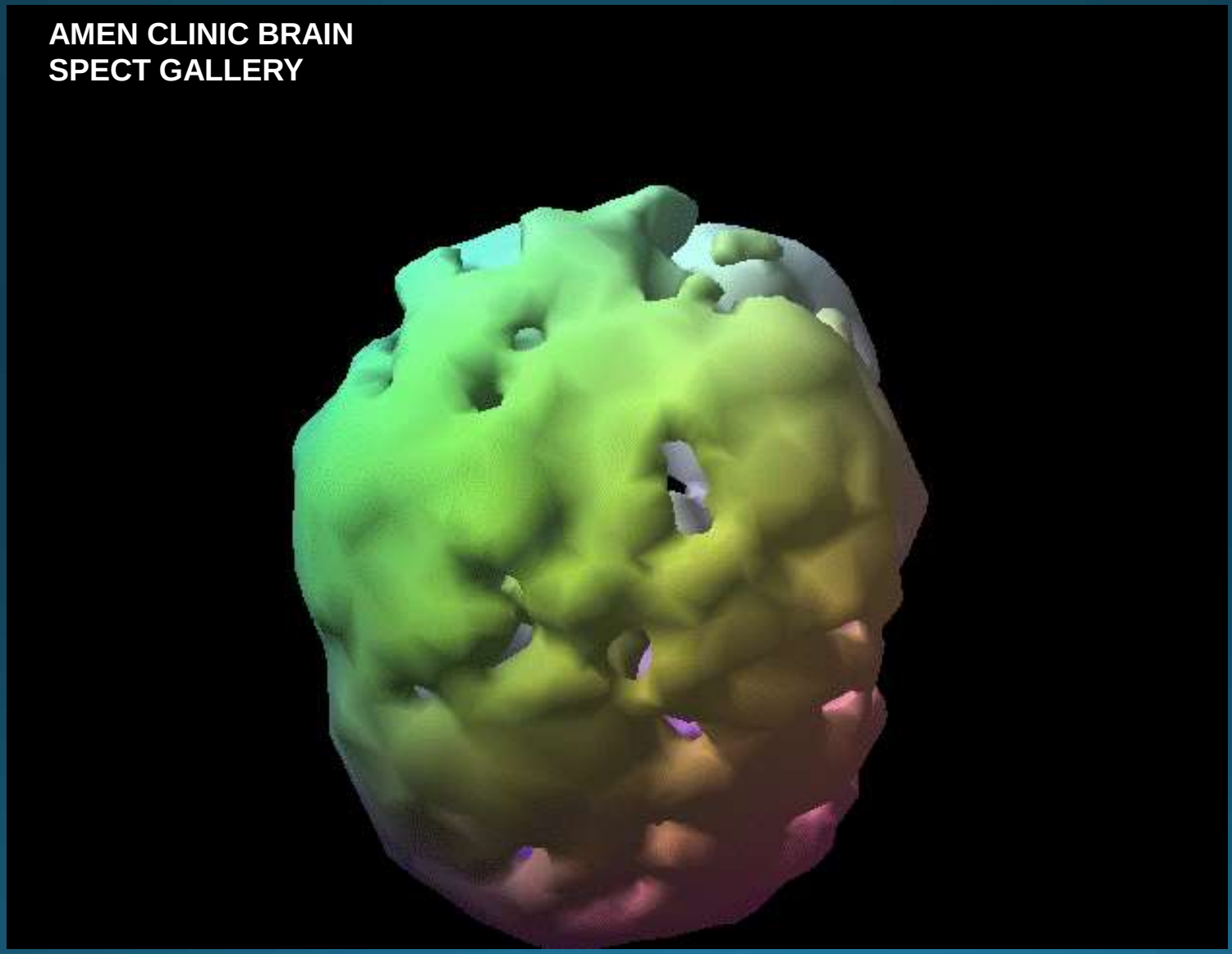
- Where the brain is stimulated, it grows in complexity.
- One can detect where the brain is active by imaging techniques.
- Most of these techniques measure neural metabolism of glucose.

BRAIN IMAGING

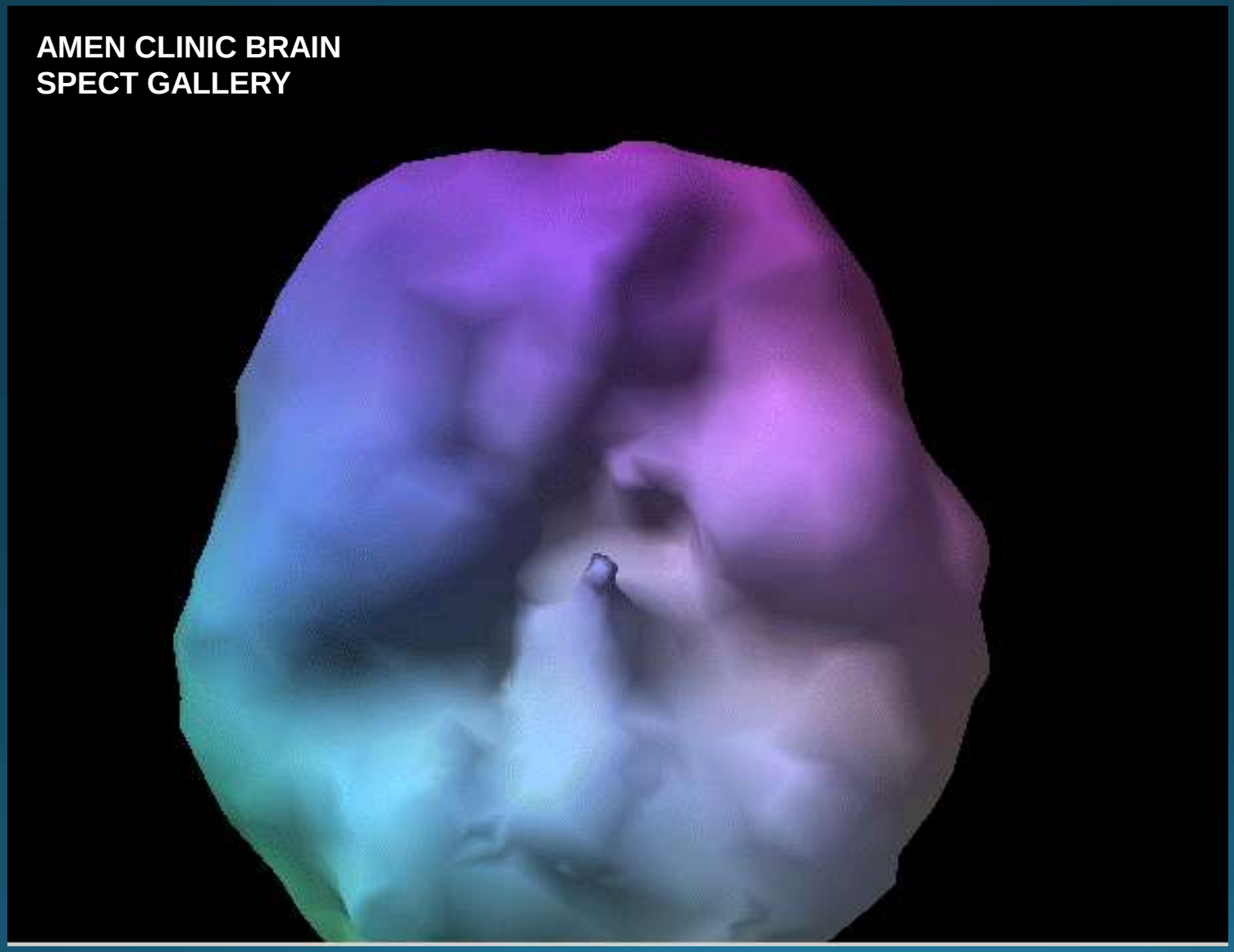
Healthy brain from the top



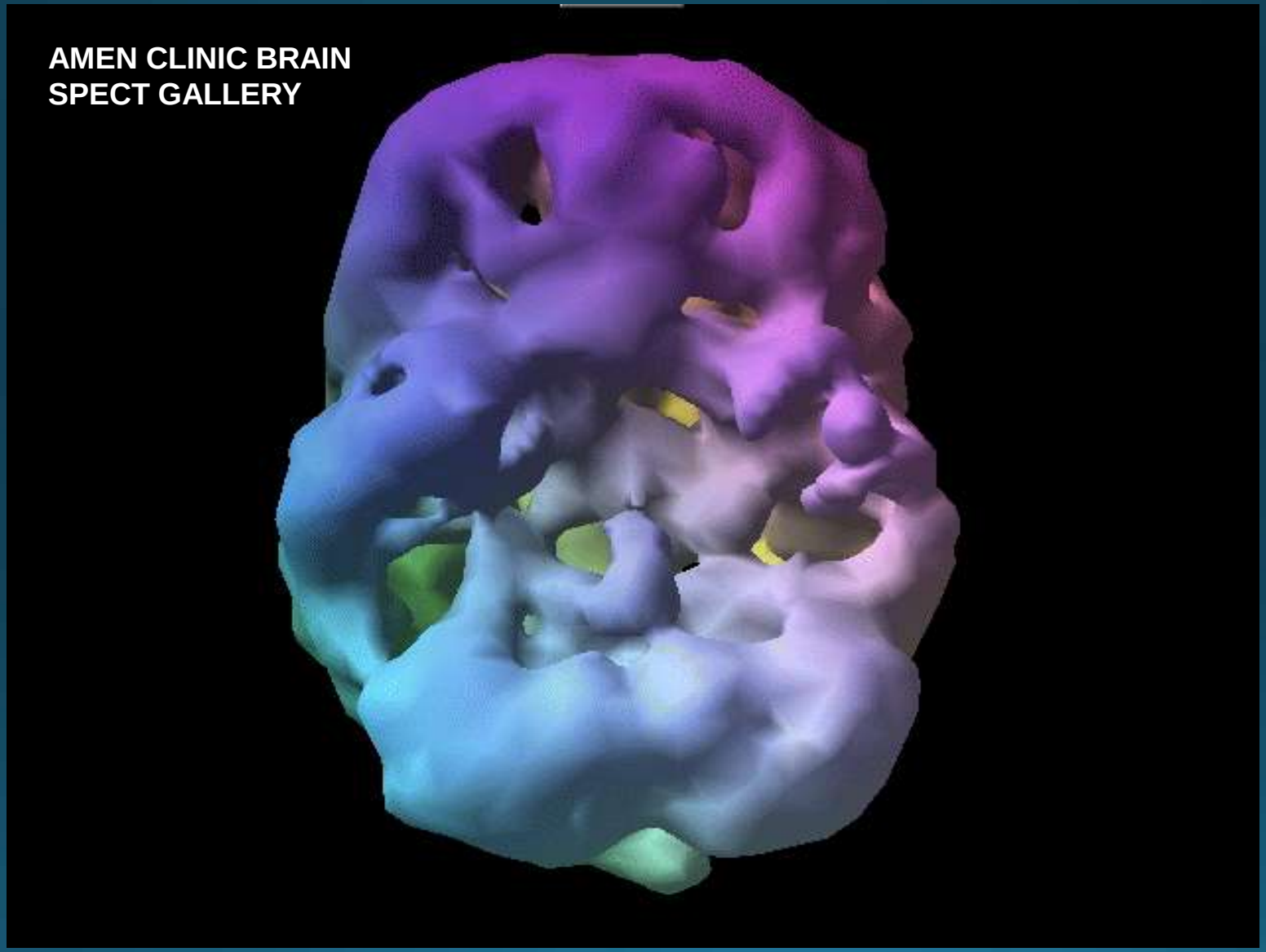
Drug user's brain from the top



Healthy brain from the underside

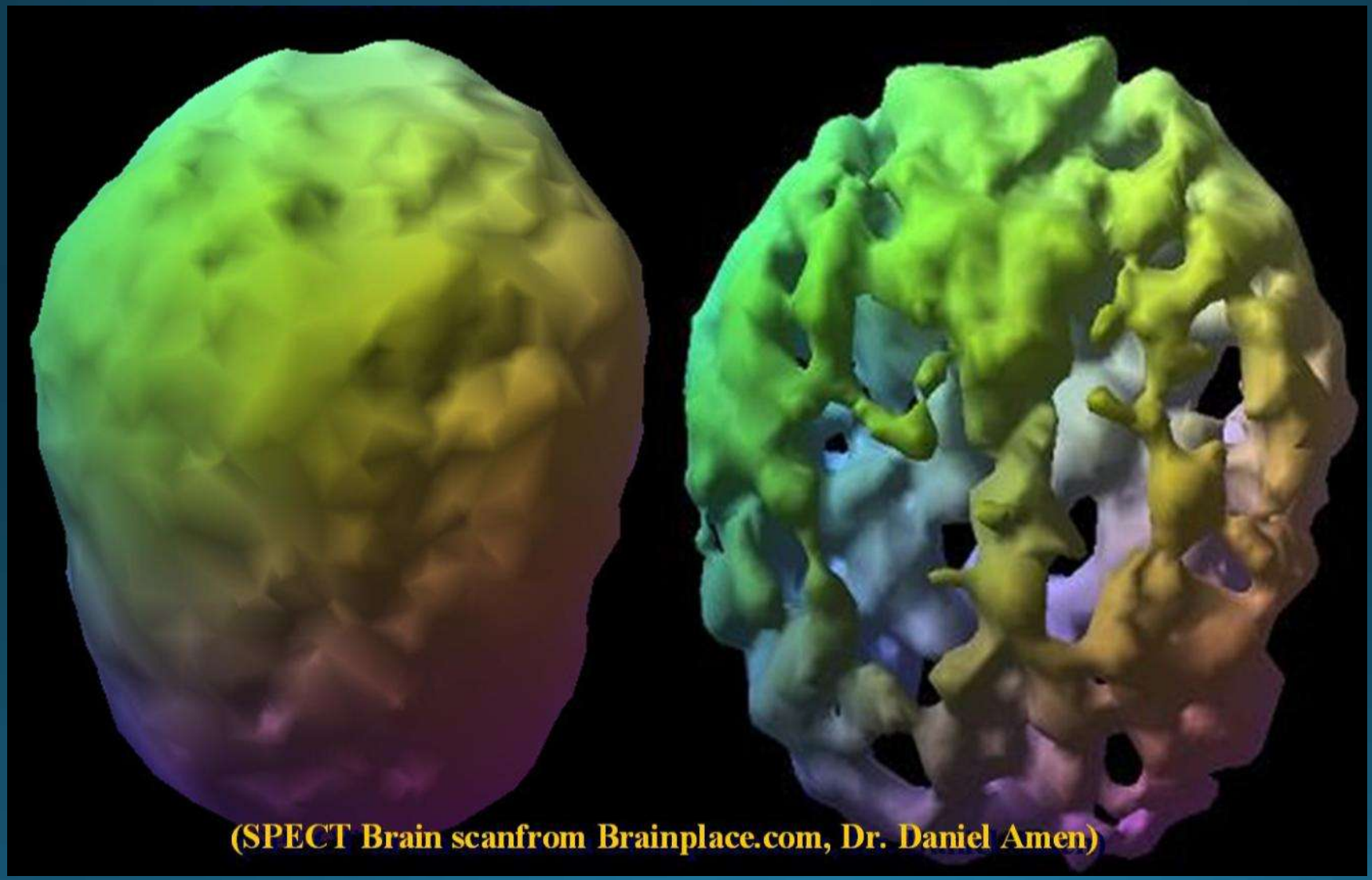


Drug user's brain from the under side

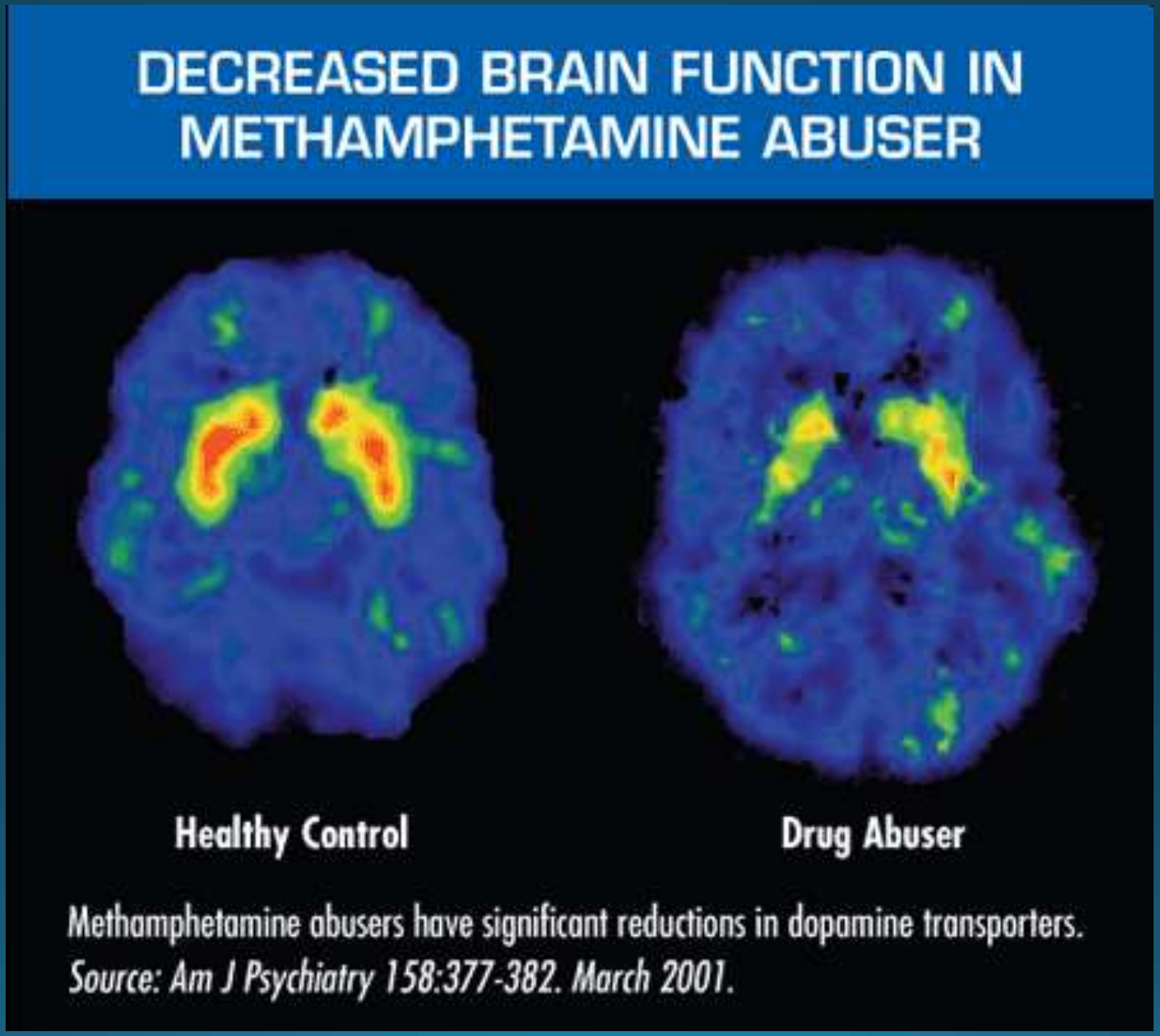


http://www.amenclinic.com/bp/spect_rotations/viewimage.php?img=da_CS.gif

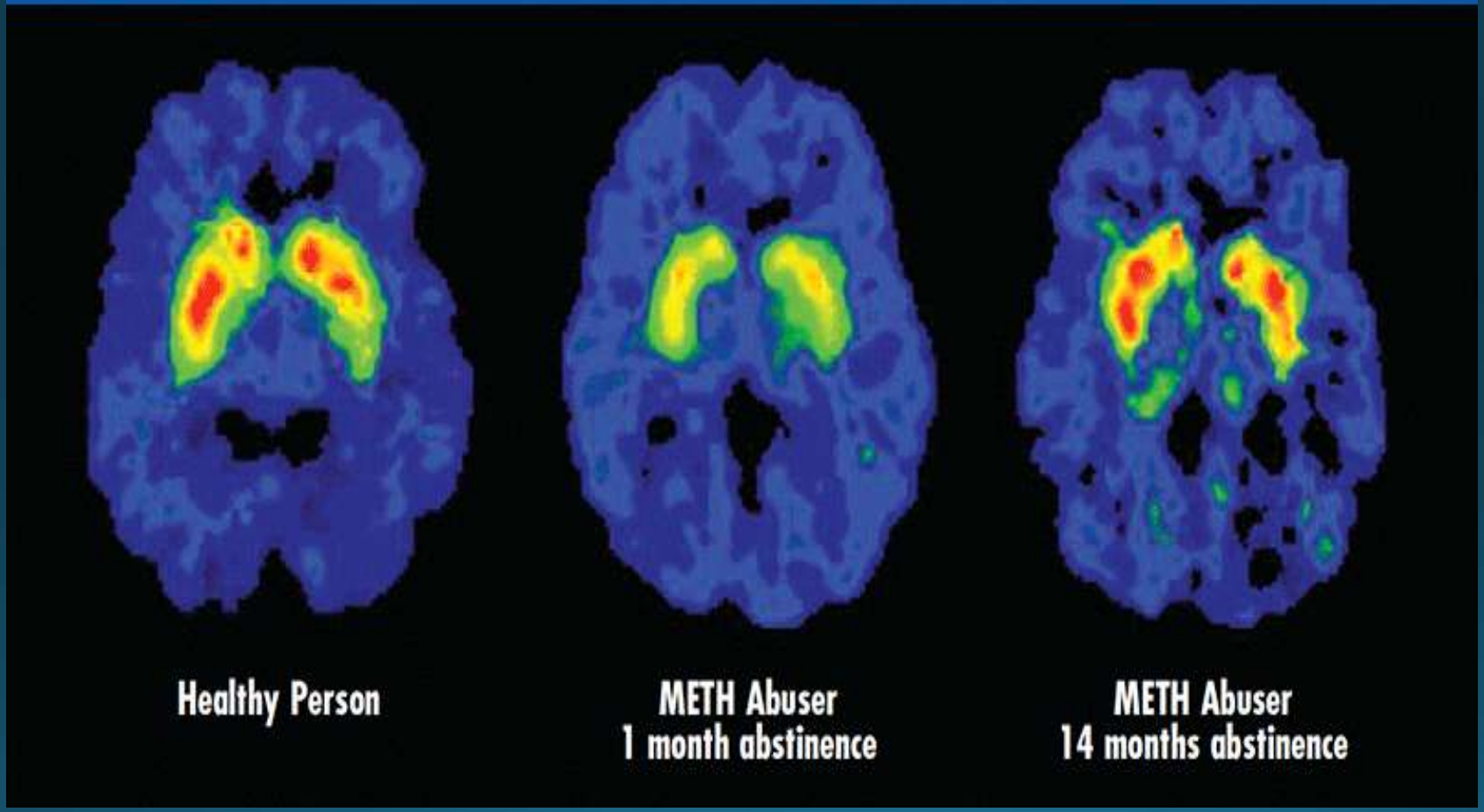
A “normal” brain and the brain of a person with 7 years of opiate use



The meth user's brain (drug free) shows lower levels of dopamine because the brain has learned how to accommodate the high levels of artificially induced dopamine.



BRAIN RECOVERY WITH PROLONGED ABSTINENCE



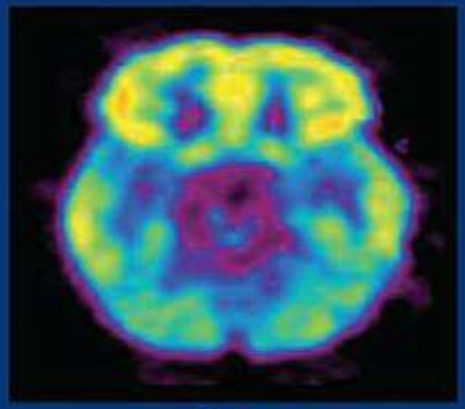
Brain Functioning Under Other Insults - Similar to Addiction

- The long term effects of substance use and even long term untreated depression can reduce frontal lobe functioning in the human brain.

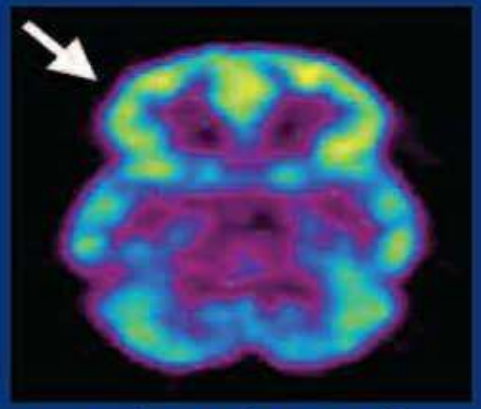
- The frontal lobes are where planning, executive functions, emotion management, and reasoning occurs – AND this is the area of the brain that *most needed for recovery activities*.

- In addition, head injuries can produce similar effects on the frontal lobes.

DECREASED BRAIN METABOLISM IN *PERSON WHO ABUSES DRUGS*

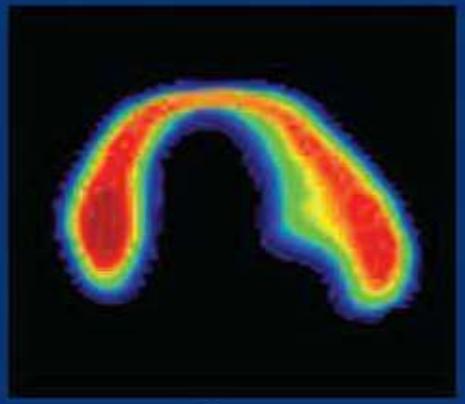


Healthy Brain

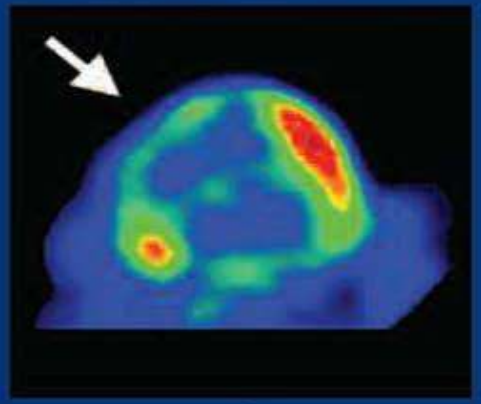


Diseased Brain/Cocaine Abuser

DECREASED HEART METABOLISM IN *HEART DISEASE PATIENT*



Healthy Heart

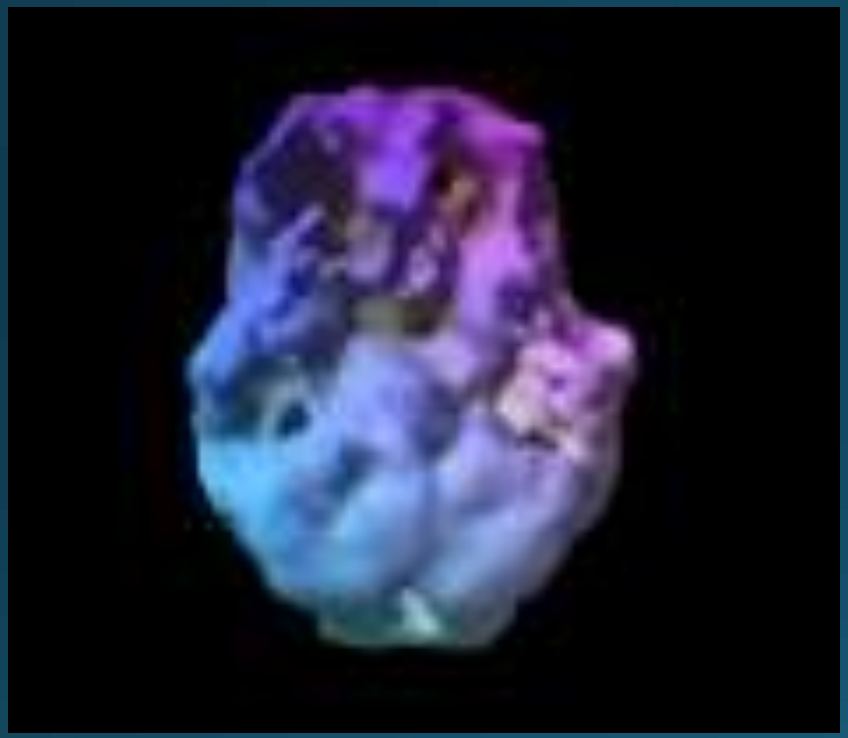


Diseased Heart

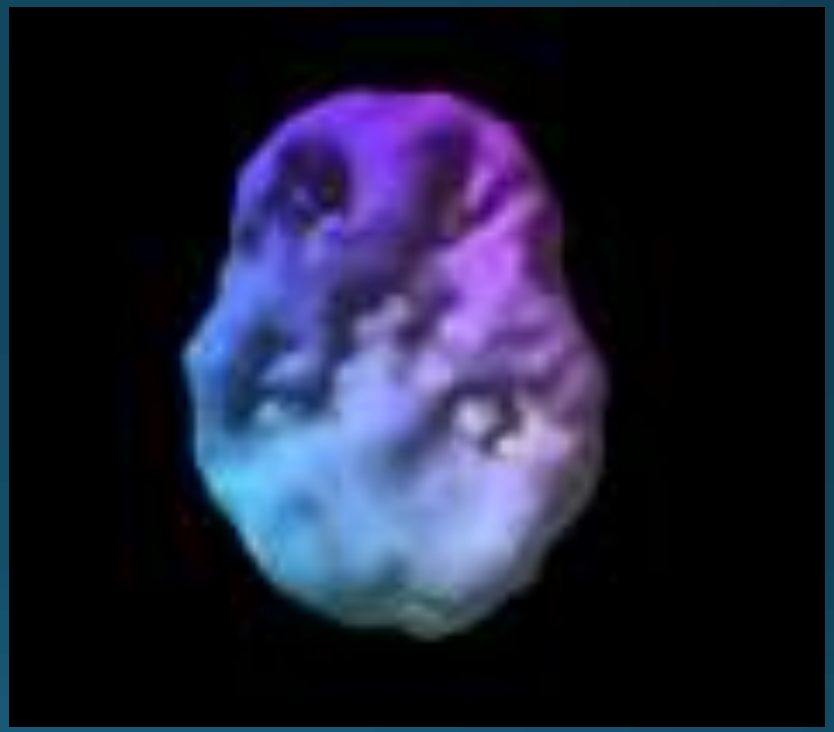
Are the changes from drug use permanent?

- Nope. Yep.
- There is increasing evidence of brain recovery from certain kinds of addiction.
- Long term heavy alcohol use results in some permanent damage and alcohol is perhaps the most harmful drug to the CNS.
- However, much of the damage done by alcohol use can be either restored or the brain can develop compensations for damaged areas.
- Even with methamphetamine, there is evidence of correcting earlier CNS damage.
- However, fundamental neurochemical "imbalances" that were there before the addiction, may still need attention.

Imaging the underside: Extensive HX Alcohol and Cocaine – Before and After TX

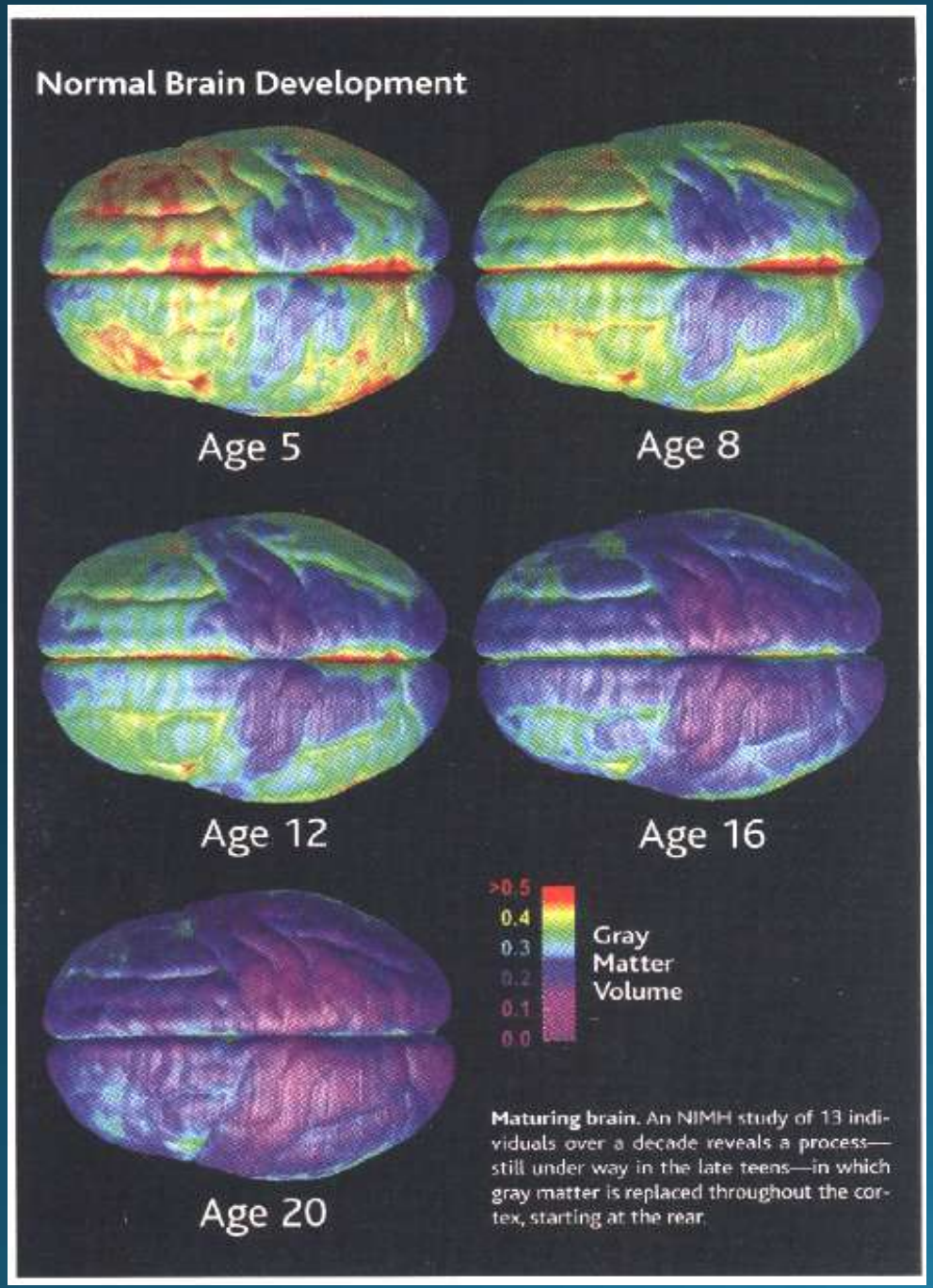


Before



After

Developmental Factors



This set of images, a composite of 13 brains during development, shows how the cortex goes through changes during adolescence. The purple color shows the replacement of gray matter in the cortex throughout development. By age 20, the brain is essentially complete in cortical development.
(Science, 2002).

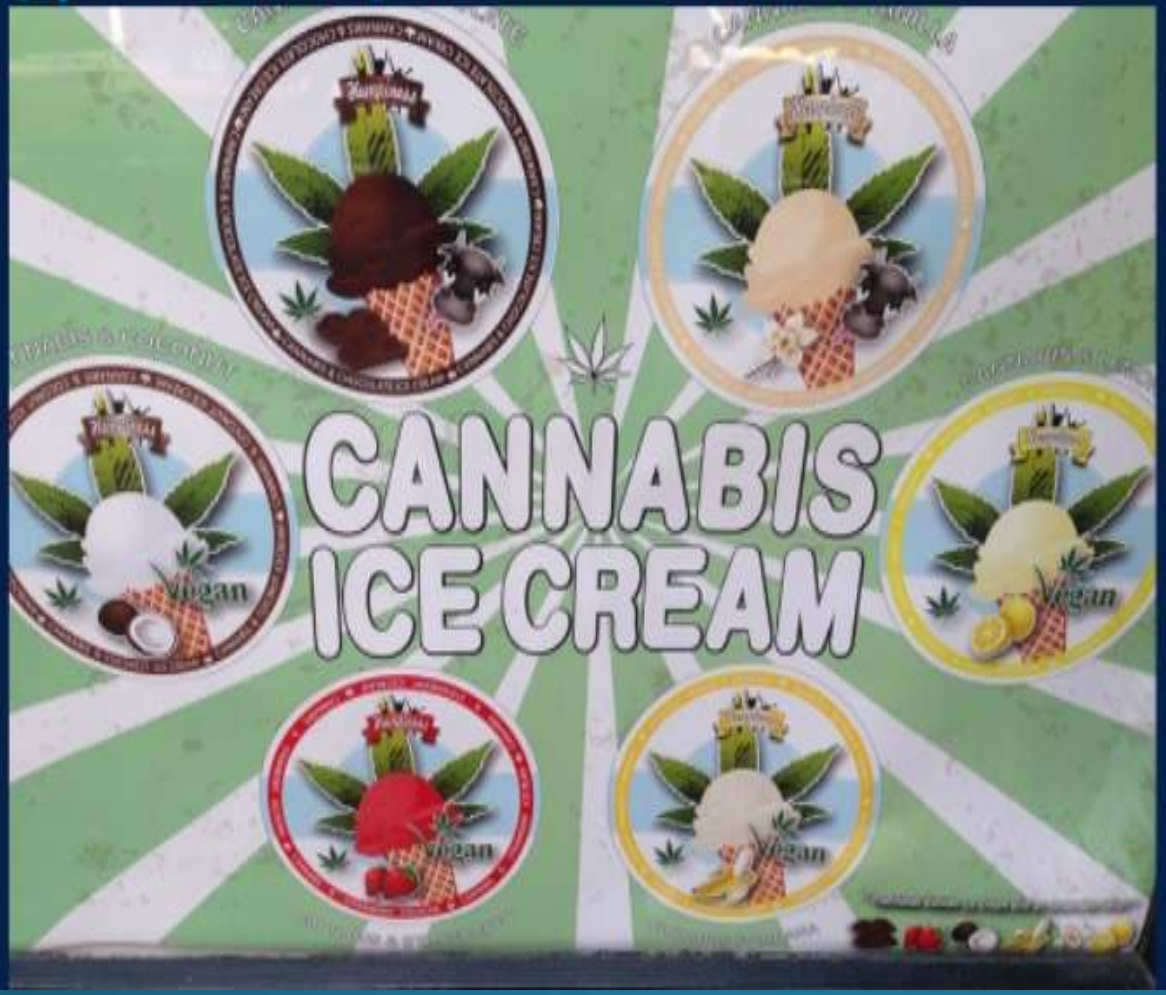
Threats from the World

- Our environment provides cues and stimuli that trigger our responses and reactions.
- New input is "compared" to what the brain has stored in its automatic response library.
- Most of these automatic responses arise from the brain stem.
- The higher brain areas can modify and even dampen those automatic responses – IF the brain has developed these areas.

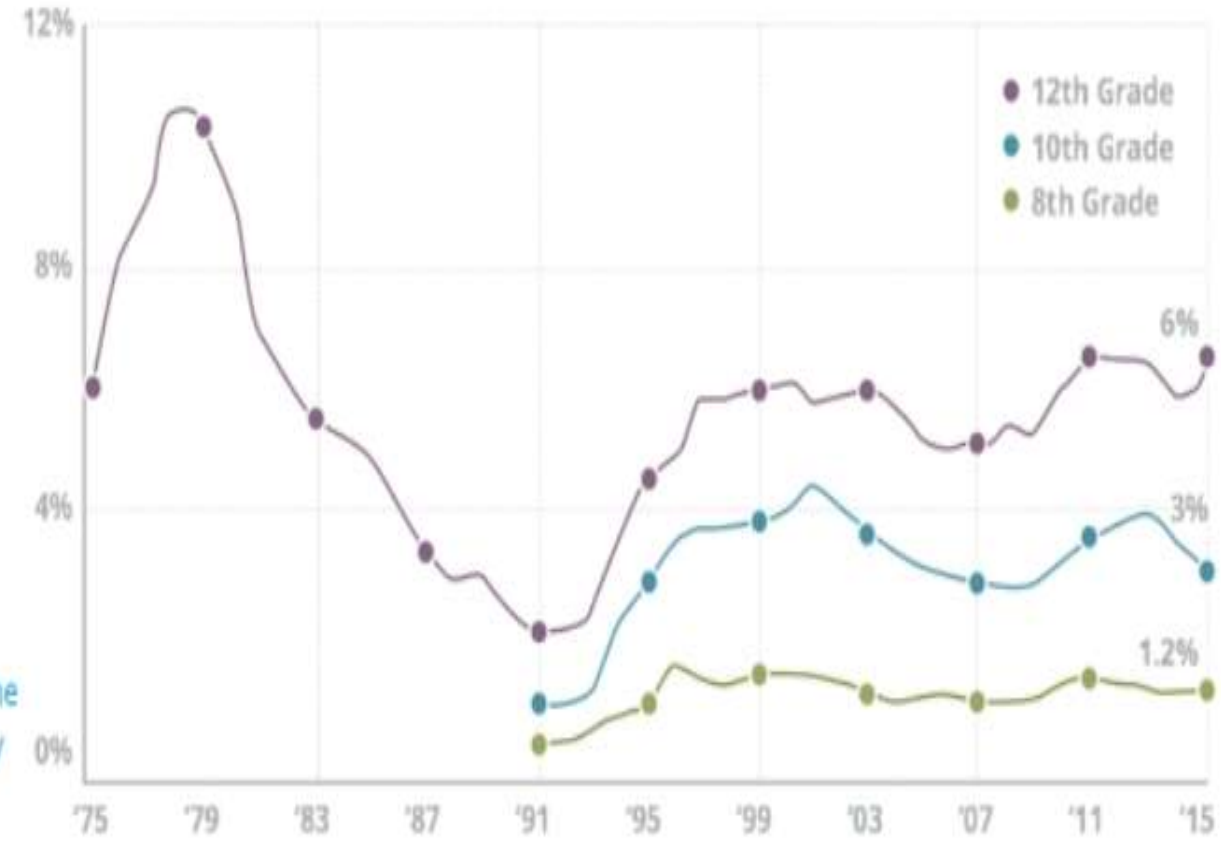
Our Culture

Access:

I scream, you scream, we all scream for...

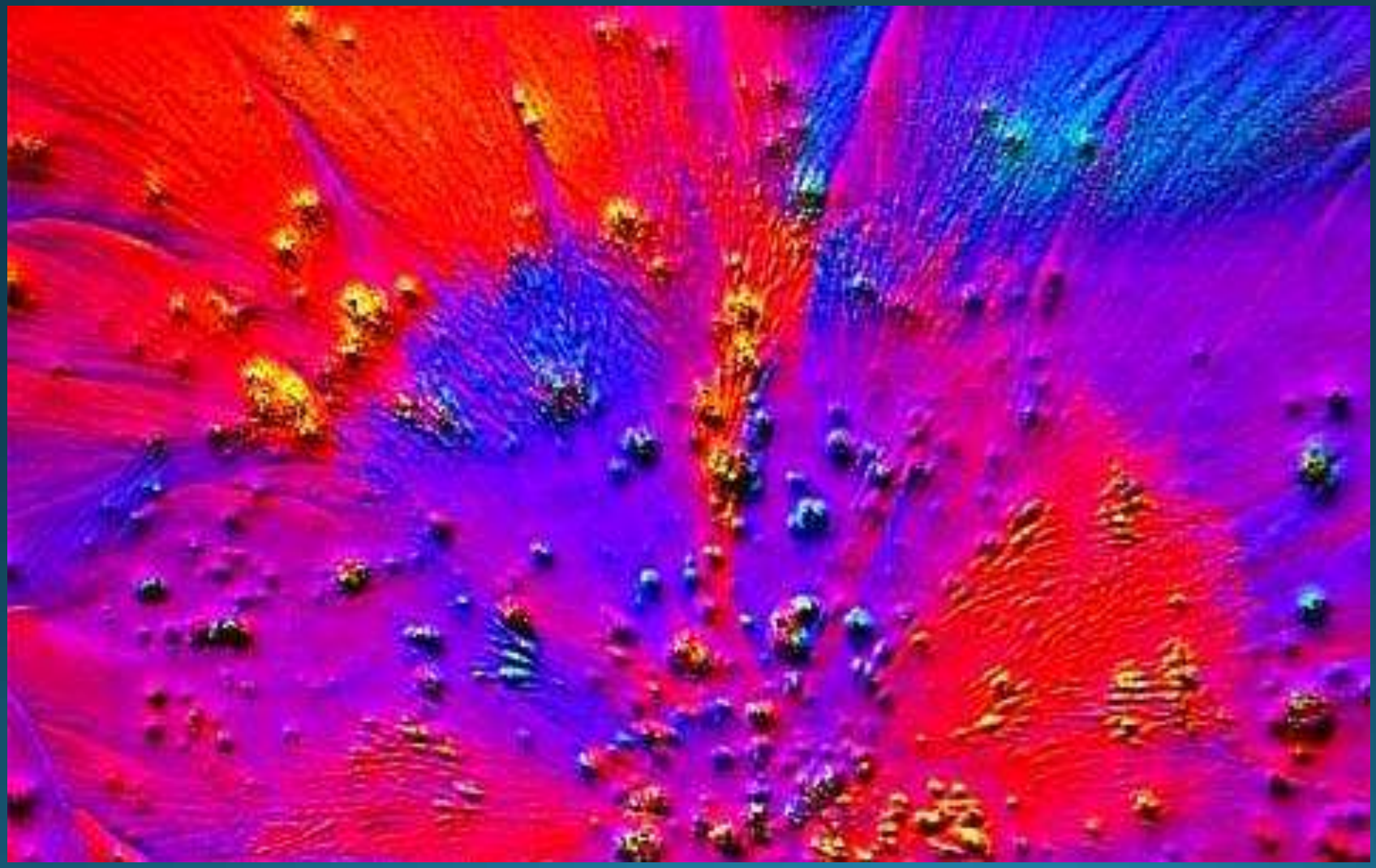


% Who Use Daily



Monitoring the Future Survey 2015

INTERVENTIONS




ADDICTION?
We Can Help!

How Healthcare Providers View It

Substance Use Disorder Diagnostic Criteria, DSM-V

More use than intended	Excessive time spent in acquisition
Unsuccessful efforts to cut down	Craving for the substance
Activities given up because of use	Continued use despite consistent social or interpersonal problems
Failure to fulfill major role obligations	Tolerance*
Use despite negative effects	Withdrawal*
Recurrent use in hazardous situations	

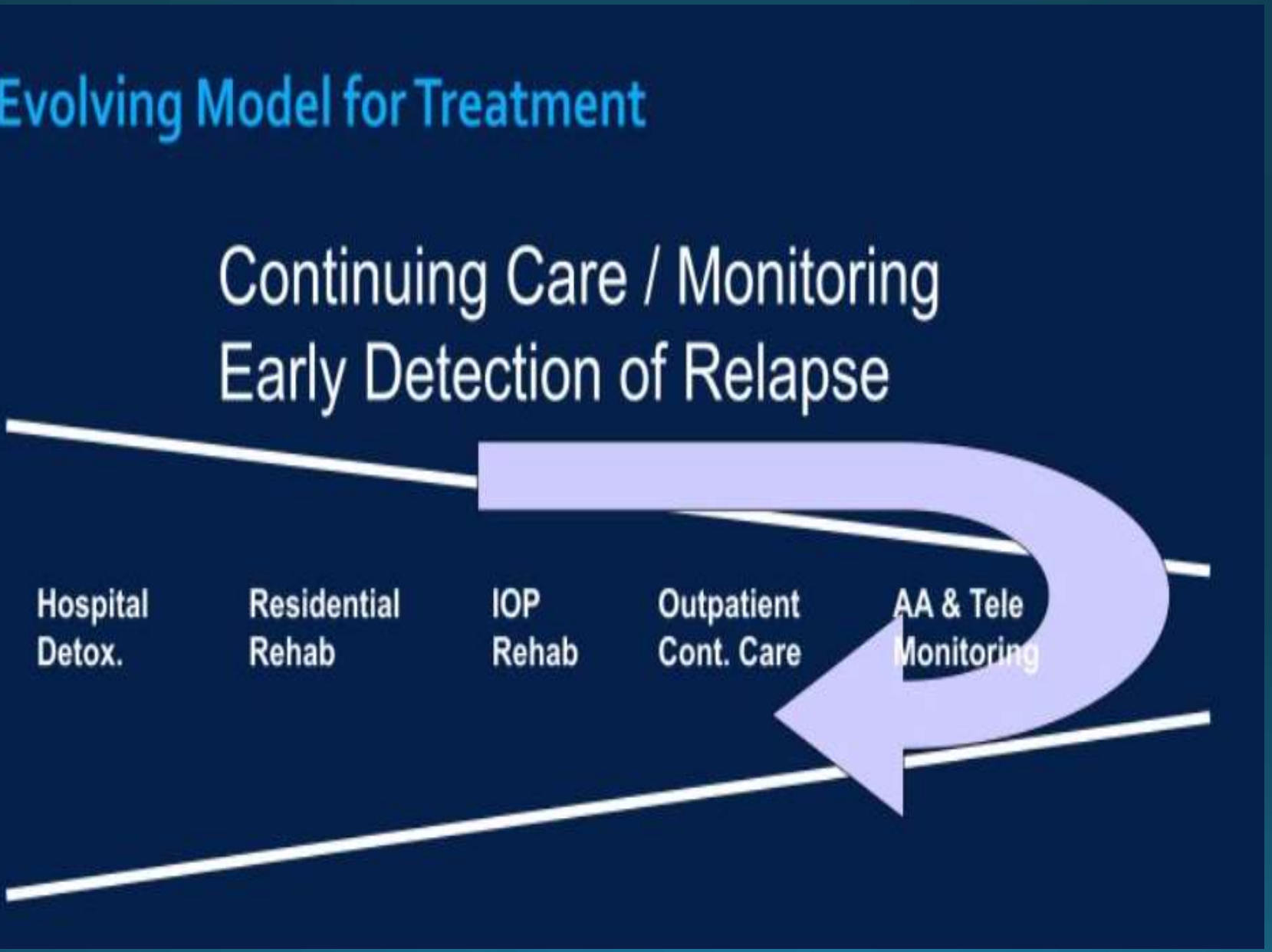
Severity measured by number of symptoms; 2-3 mild, 4-6 moderate, 7-11 severe

- These do not apply if the medication is prescribed and no other diagnostic criteria are met

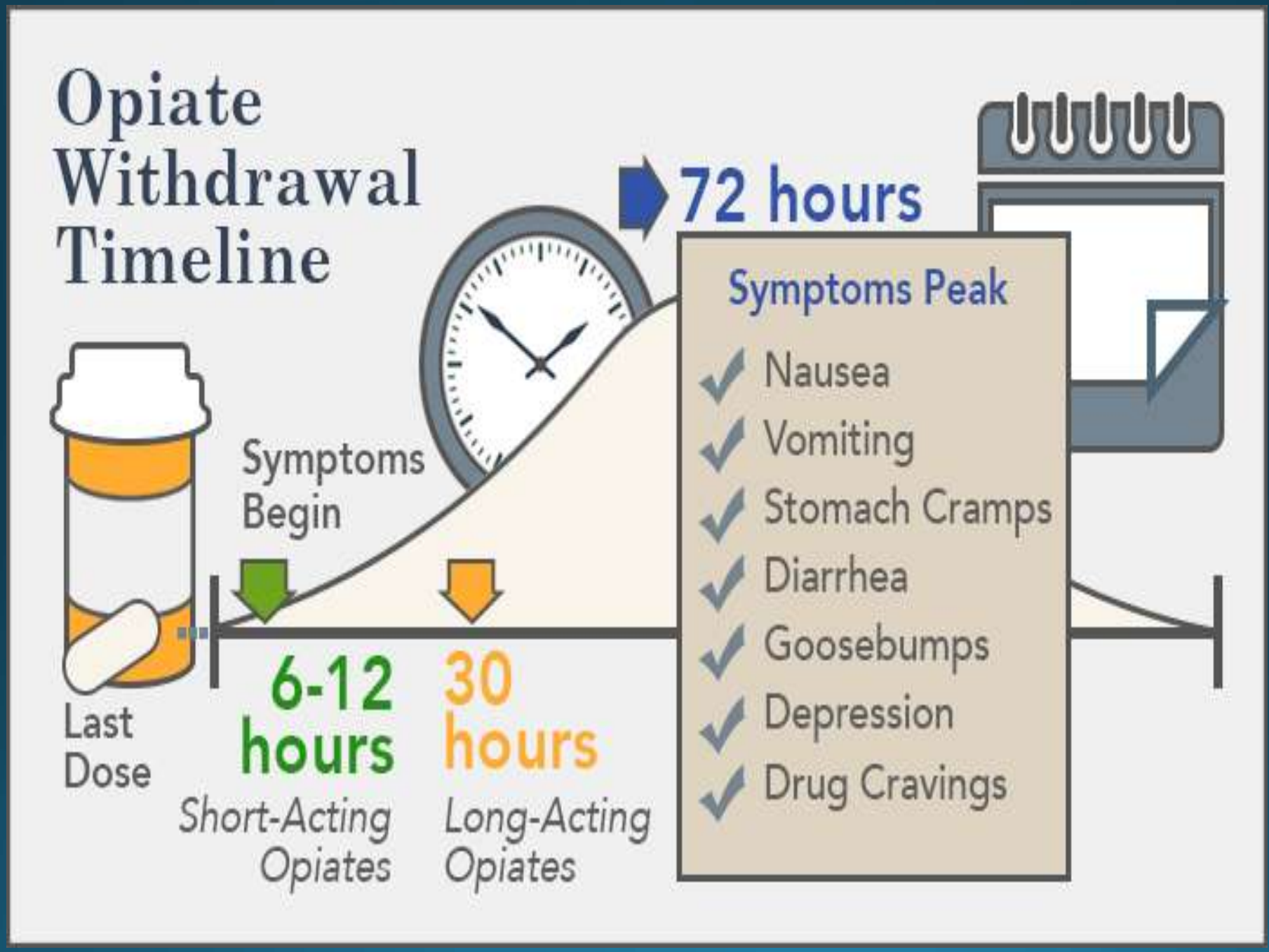
#RxSummit

NATIONAL RX DRUG ABUSE & HEROIN SUMMIT

Evolving Model for Treatment




TIME
TO
DETOX


Opiate Withdrawal Timeline
72 hours
Symptoms Peak
Nausea
Vomiting
Stomach Cramps
Diarrhea
Goosebumps
Depression
Drug Cravings
Symptoms Begin
Last Dose
6-12 hours
Short-Acting Opiates
30 hours
Long-Acting Opiates

THE PAIN OF WITHDRAWAL

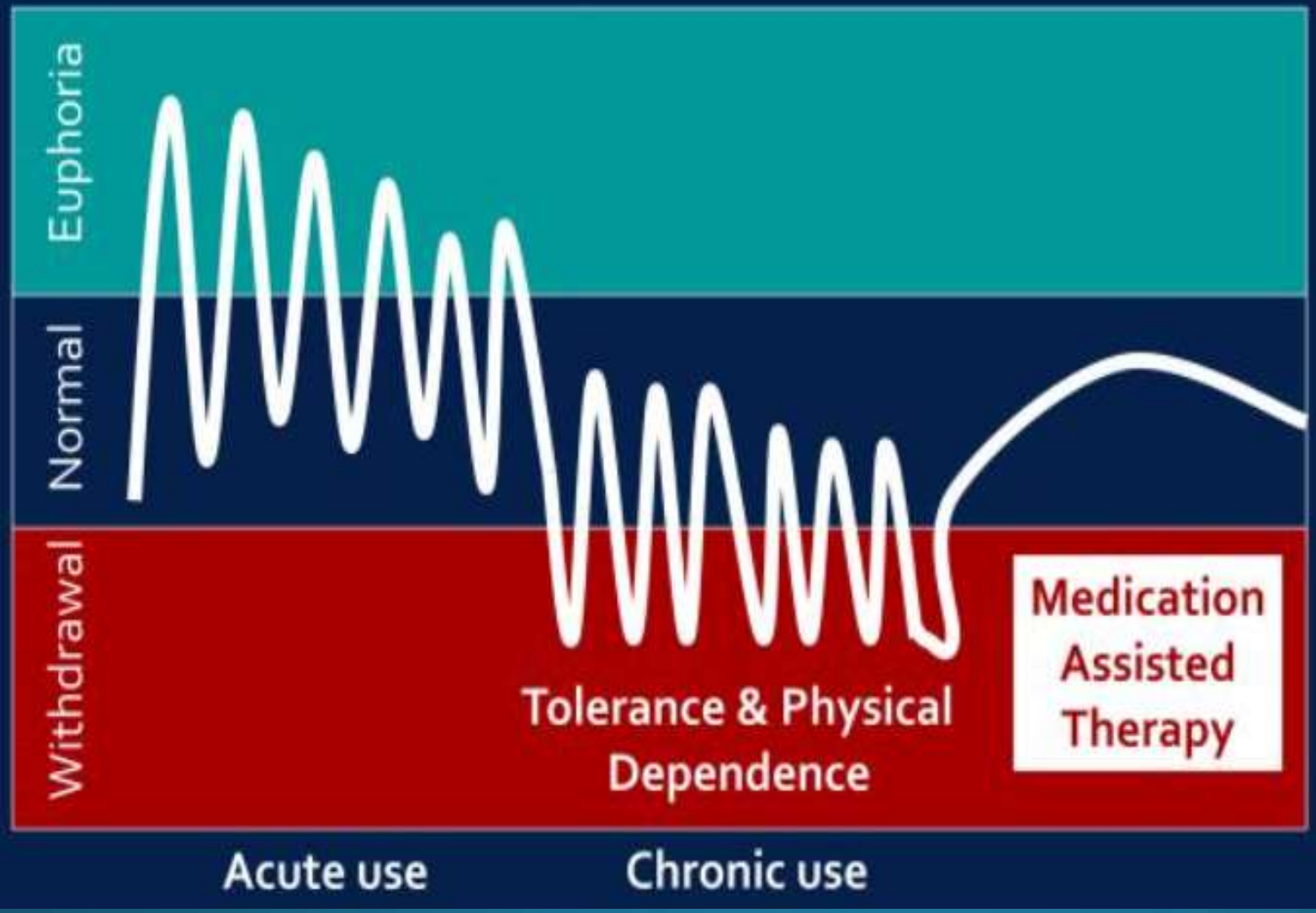
M.A.T. MEDICALLY ASSISTED TREATMENT

TABLE 2 Comparison of FDA-approved medications for the treatment of opioid use disorders

Medication	Mechanism of action at μ-opioid receptor	Phase of treatment	Formulations	Dosages commonly used	Adverse effects	Regulations/ availability
Methadone	Agonist	Detoxification, maintenance	Oral	Detoxification: 20 - 40 mg/d, maintenance: 80 - 120 mg/d	Respiratory suppression, sedation, prolonged QTc, constipation, hyperhidrosis, sexual dysfunctions	Only available at designated federally regulated opioid treatment sites
Buprenorphine	Partial agonist	Detoxification, maintenance	Sublingual, buccal	2 - 32 mg/d	Constipation, nausea, precipitated withdrawal	Requires DATA 2000 waiver + DEA X-number, available for office-based treatment
Naltrexone	Antagonist	Relapse prevention, maintenance	Oral, intramuscular	25 - 100 mg/d PO, 380 mg/mo IM	Nausea, anxiety, insomnia, precipitated withdrawal	None, office-based treatment

Data 2000, Drug Addiction Treatment Act of 2000; DEA, Drug Enforcement Administration.

Opioid Agonist Therapy



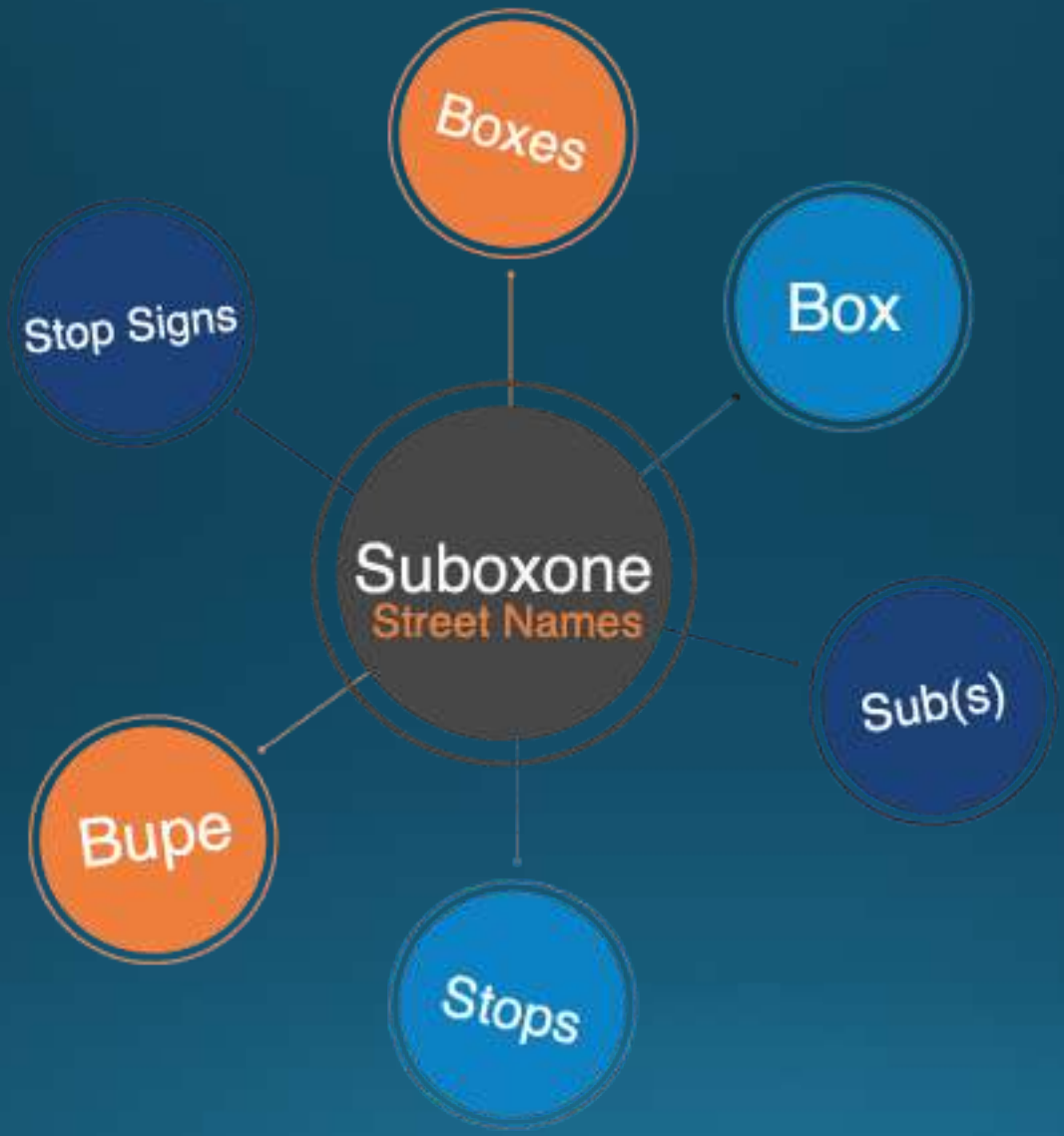

Methadone
$C_{21}H_{27}NO$
CH_3
O
CH_3
N—CH_3
H_3C


500ml e
Methadone
Hydrochloride
DTF 1mg/1ml
Oral Solution
central nervous system

How does methadone work?

- Methadone binds to the same receptor sites as other opioids (opioid agonist)
- Orally effective
- Slow onset of action
- Long duration of action
- Slow offset of action

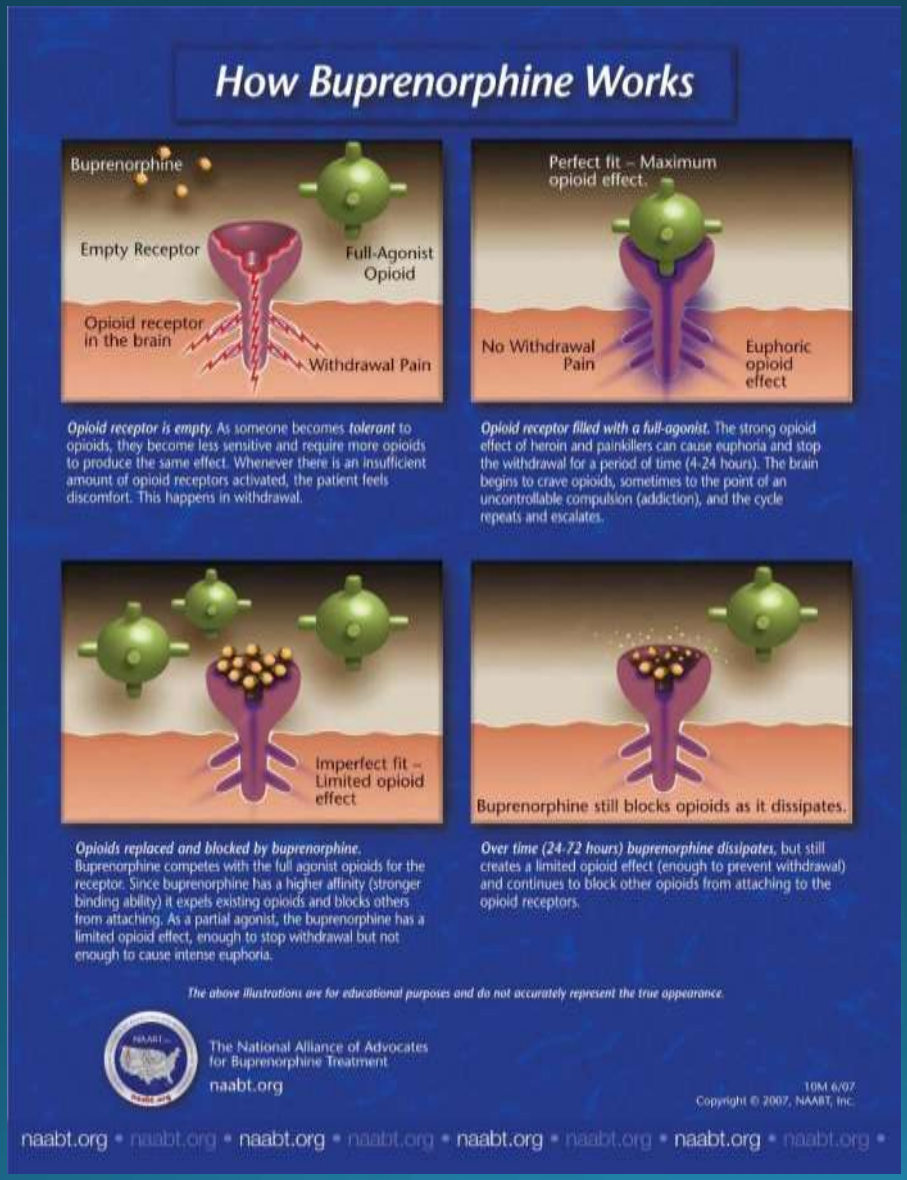
Suboxone Treatment


Boxes
Stop Signs
Box
Suboxone
Street Names
Sub(s)
Bupe
Stops

Suboxone tablets
Photo by Adam Fedorko, © 2006 Erowid.org


7 comprimés sublinguaux
SUBUTEX®
BUPRENORPHINE
8 mg
Schering-Plough

How does Suboxone work?

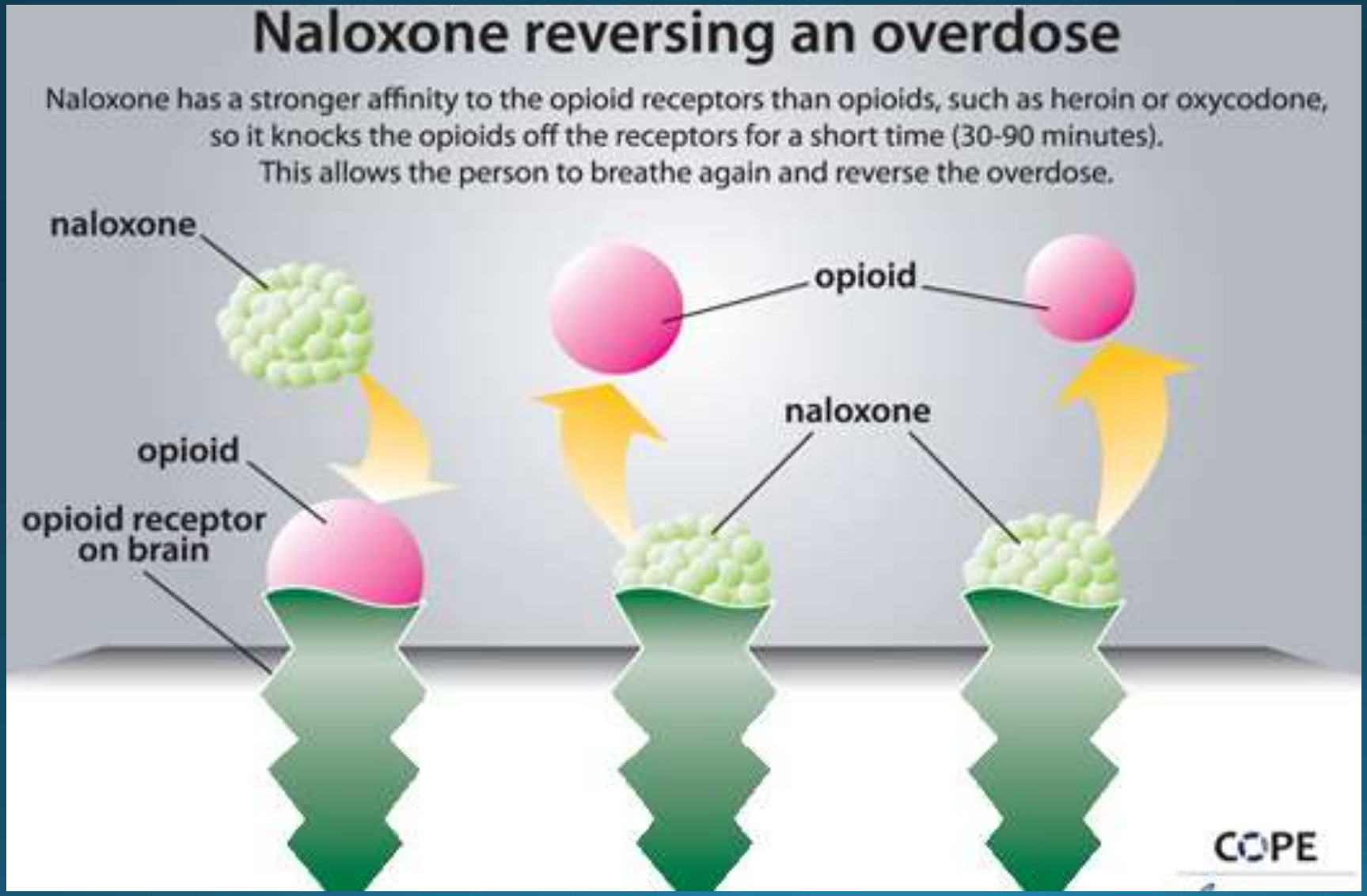


NALOXONE

Intranasal

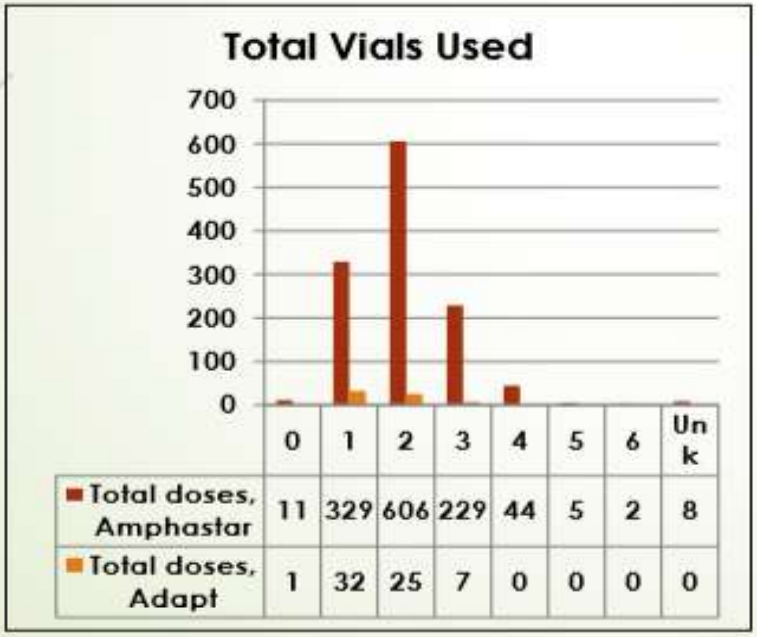
Intramuscular

What is Narcan?

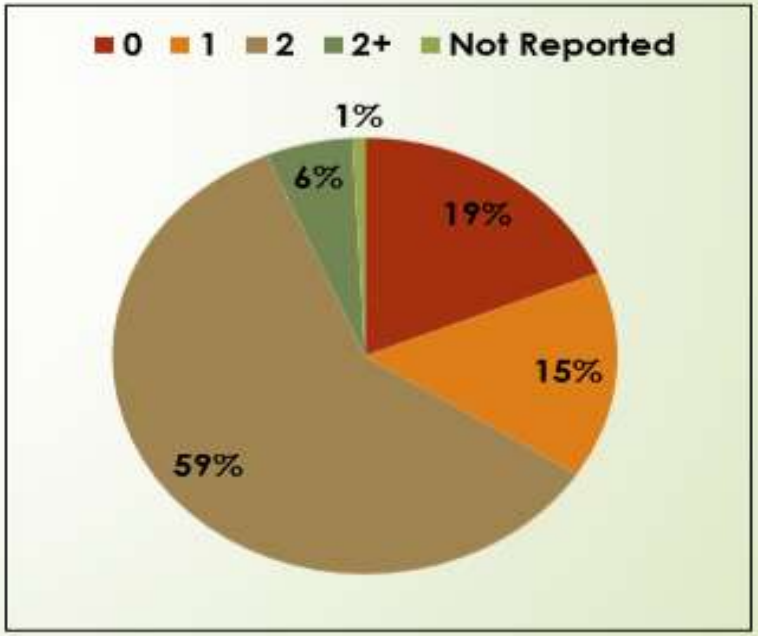


Number of Vials Used to Reverse Overdoses

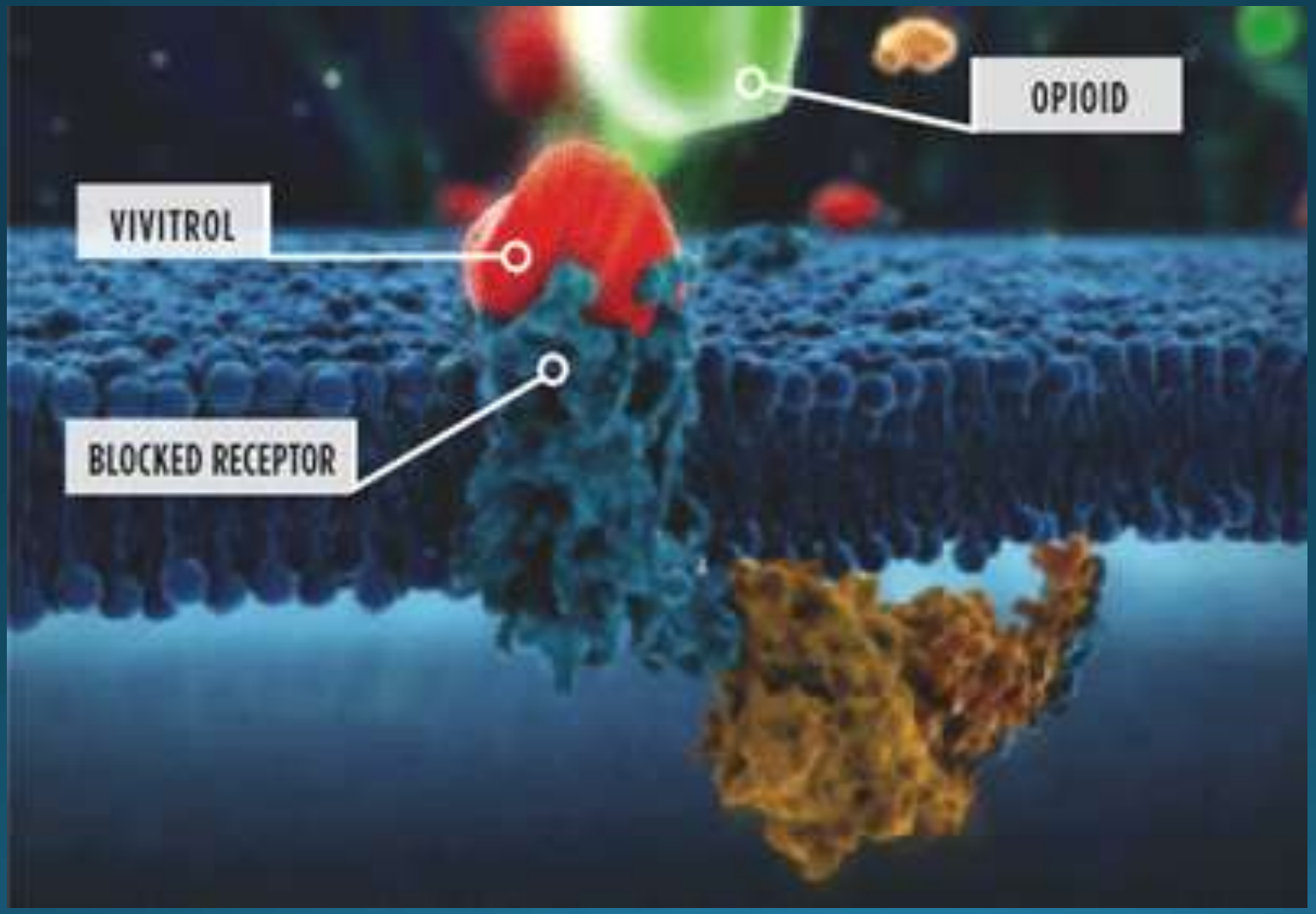
Police/Fire (First Responder, Civilian, and EMS, N = 1,299)



Community (N = 378)



What is Vivitrol (Naltrexone) ?

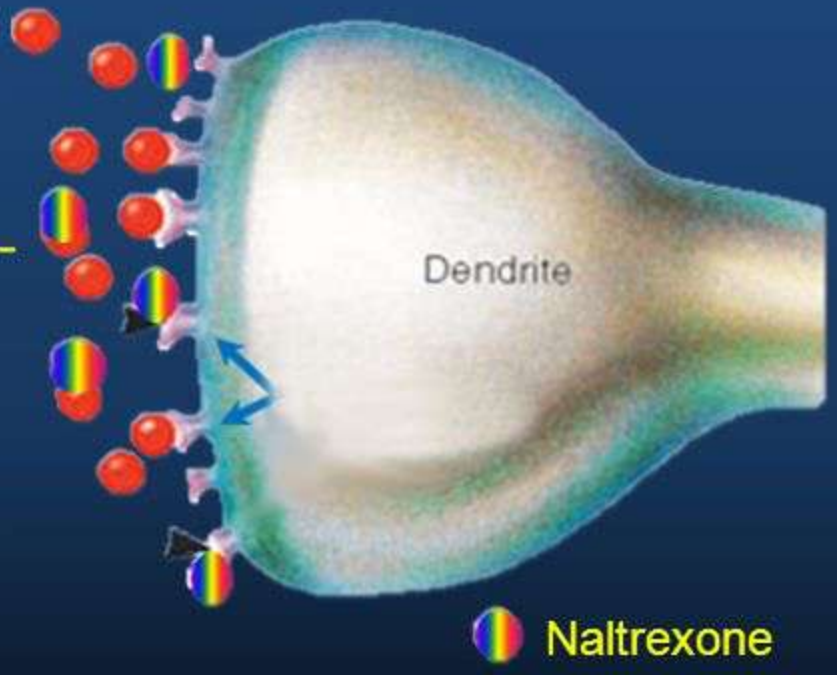


How Does Naltrexone Work?

- Naltrexone is an opioid receptor antagonist and blocks opioid receptors.

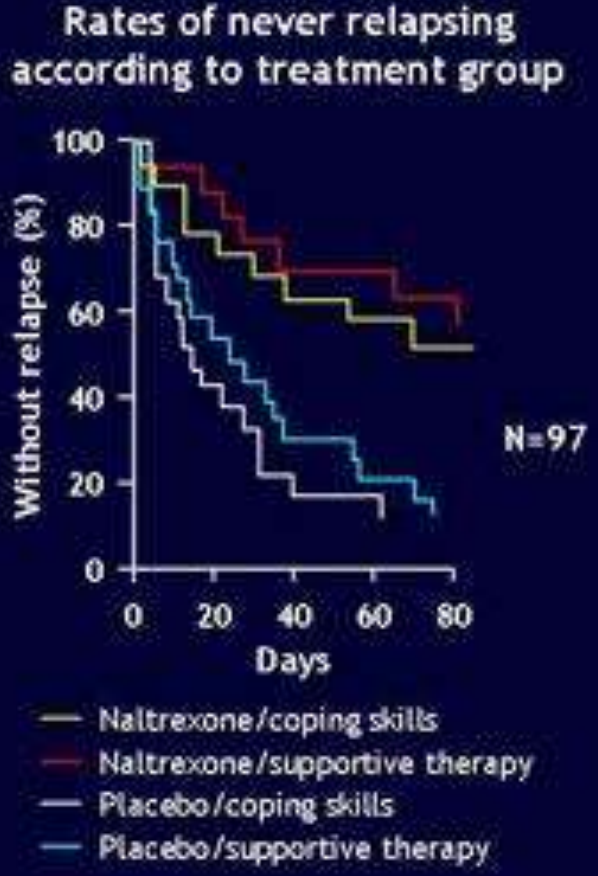
This prevents the effects of self-administered opioids.

It also diminishes release dopamine when alcohol is consumed, reducing the pleasurable effects



Oral Naltrexone in the Treatment of Alcohol Dependence

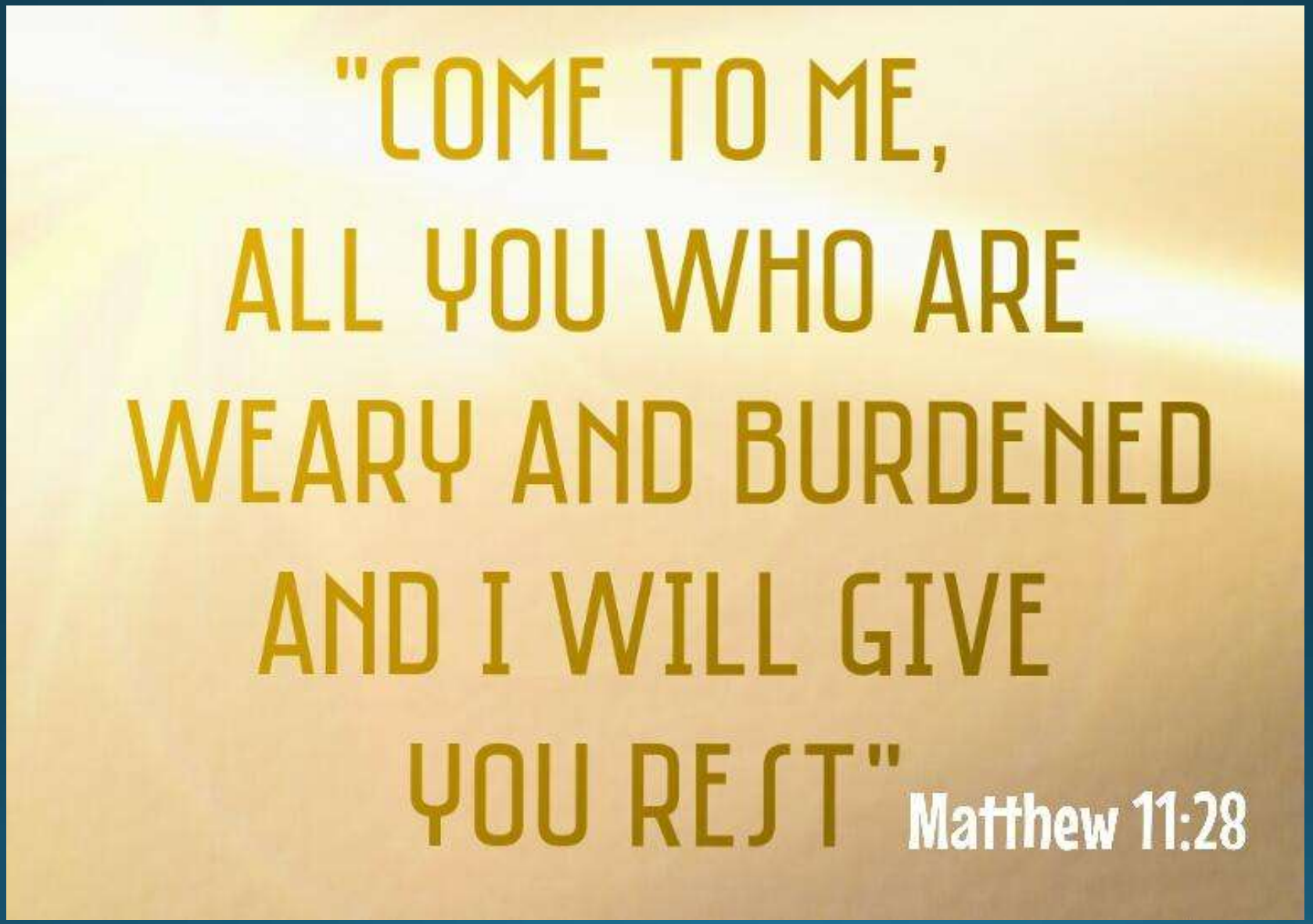
- 2×2 design (four groups)
- 97 recently abstinent alcoholics treated with placebo or 50 mg daily naltrexone and either of two psychotherapies for 12 weeks



O'Malley SS et al. *Arch Gen Psychiatry* 1992;49:881-887.

NOW FOR THE BEST NEWS OF ALL


HOPE


"COME TO ME,
ALL YOU WHO ARE
WEARY AND BURDENED
AND I WILL GIVE
YOU REST"
Matthew 11:28