Neurobiology of Addiction: What does Use of Substances do to our brains?

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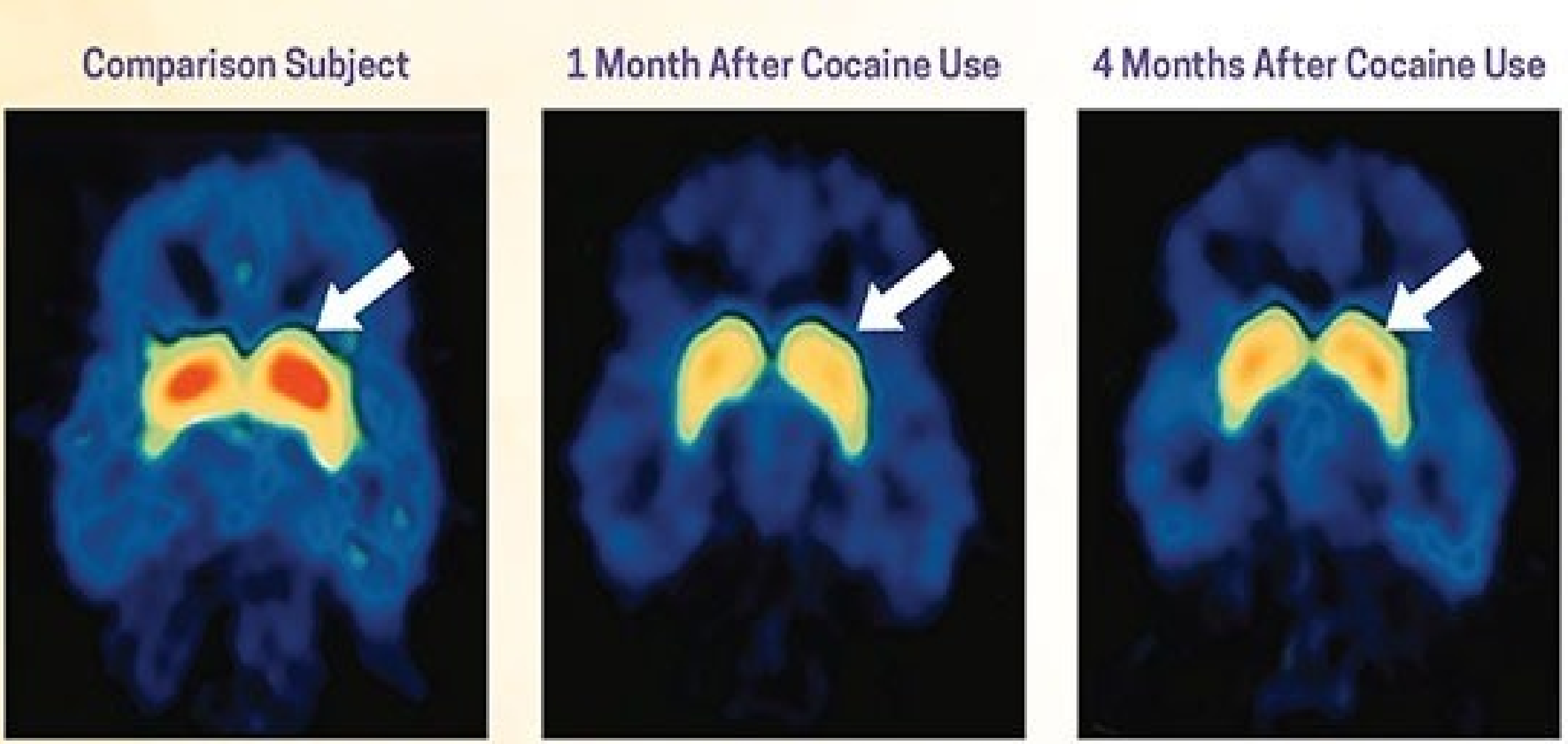
NIDA Definition of Addiction

Chronic relapsing disorder characterized by compulsive drug seeking despite adverse consequences.

Brain disorder because it involves functional changes to brain circuits involved in reward, stress and self control.

Changes may last a long time after the person stopped taking the substances.

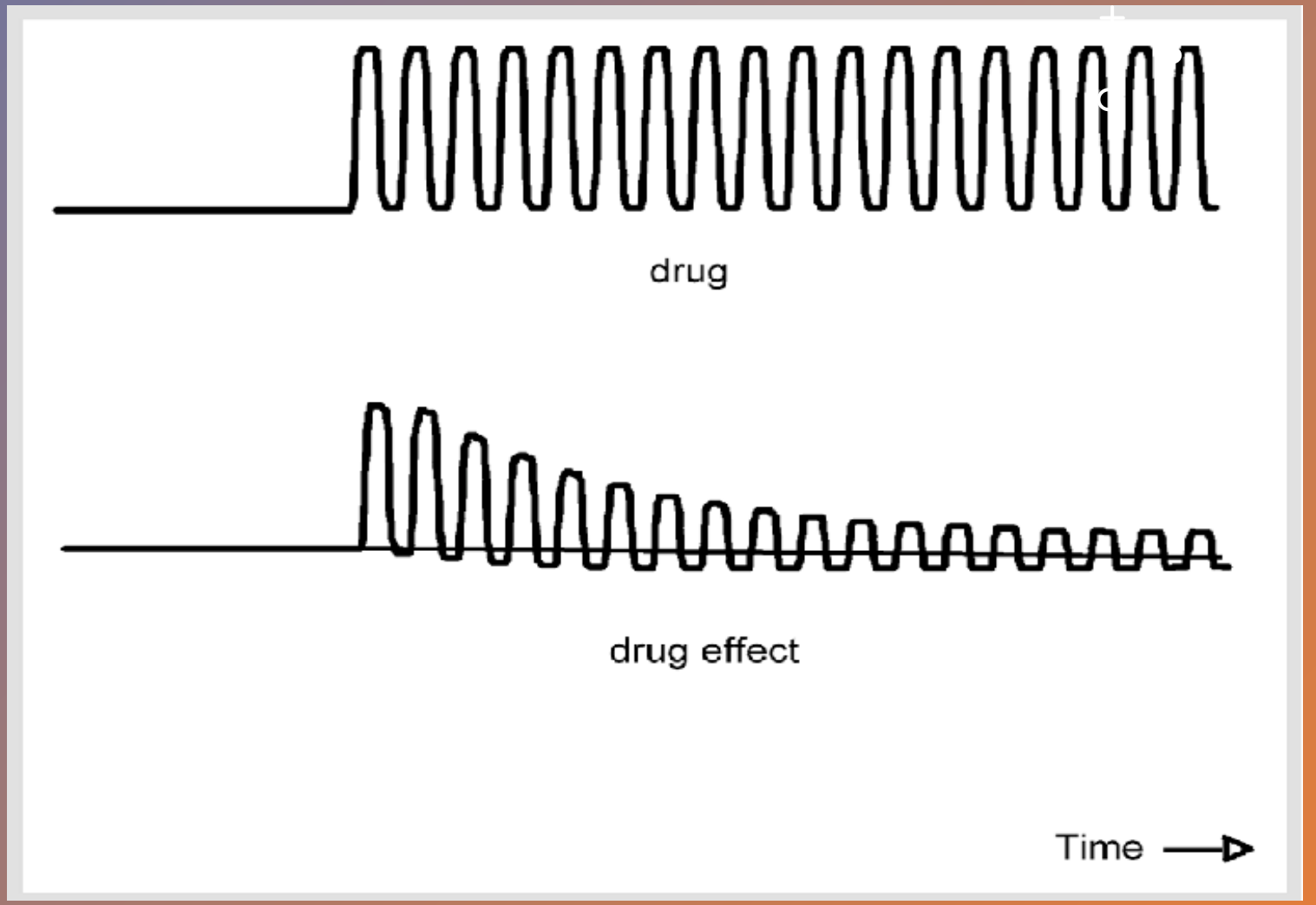


Low dopamine D2 receptors may contribute to the loss of control in cocaine users.

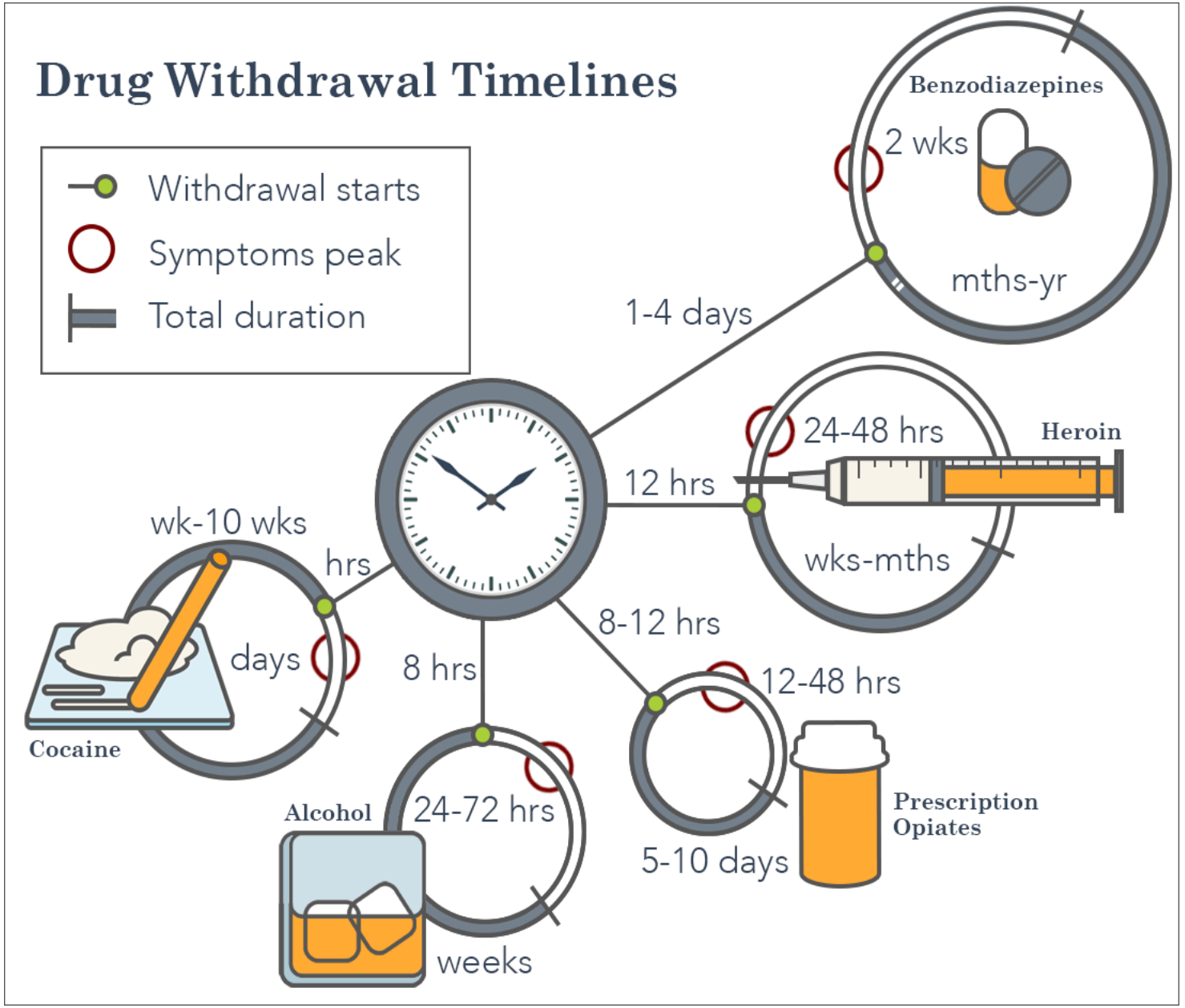
When do we call a substance is addictive?

- When repeated use of the substance causes
  - Tolerance
  - Withdrawal
  - Craving
  - Loss of Control

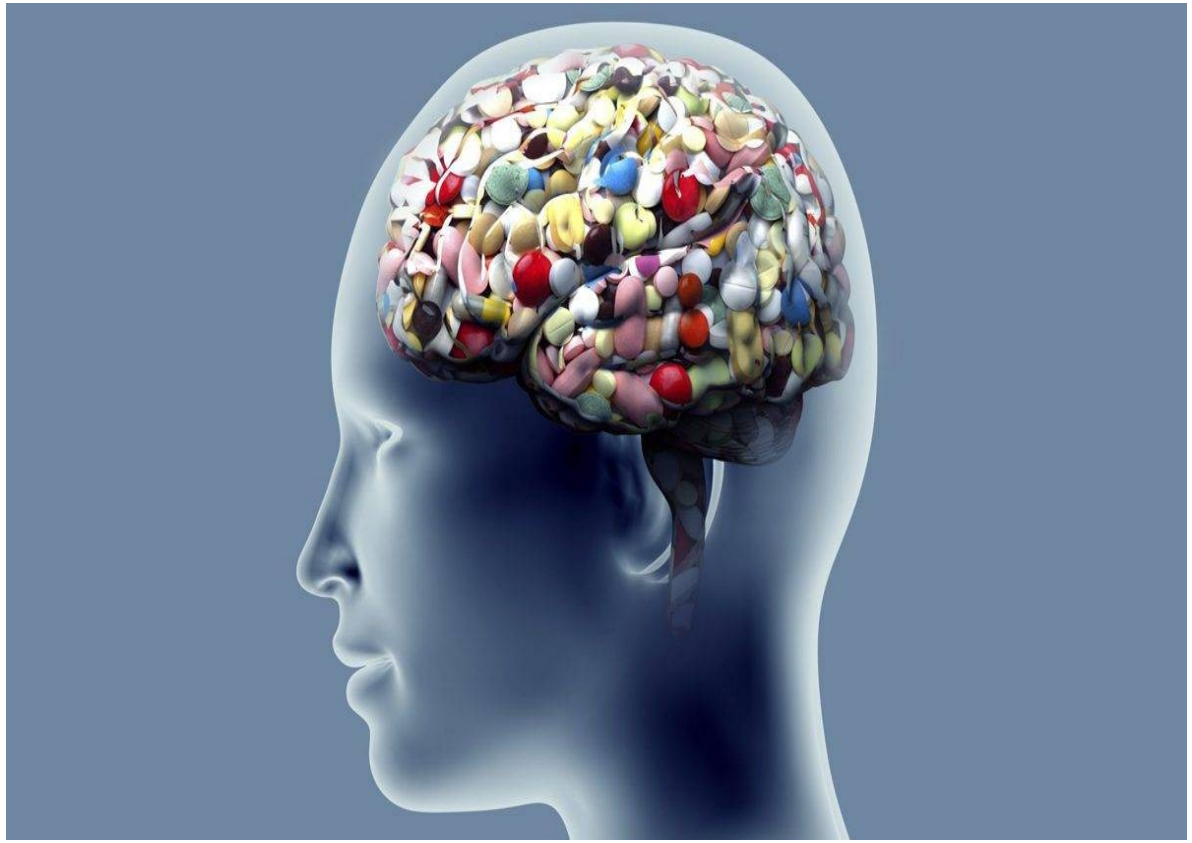
What is Tolerance?



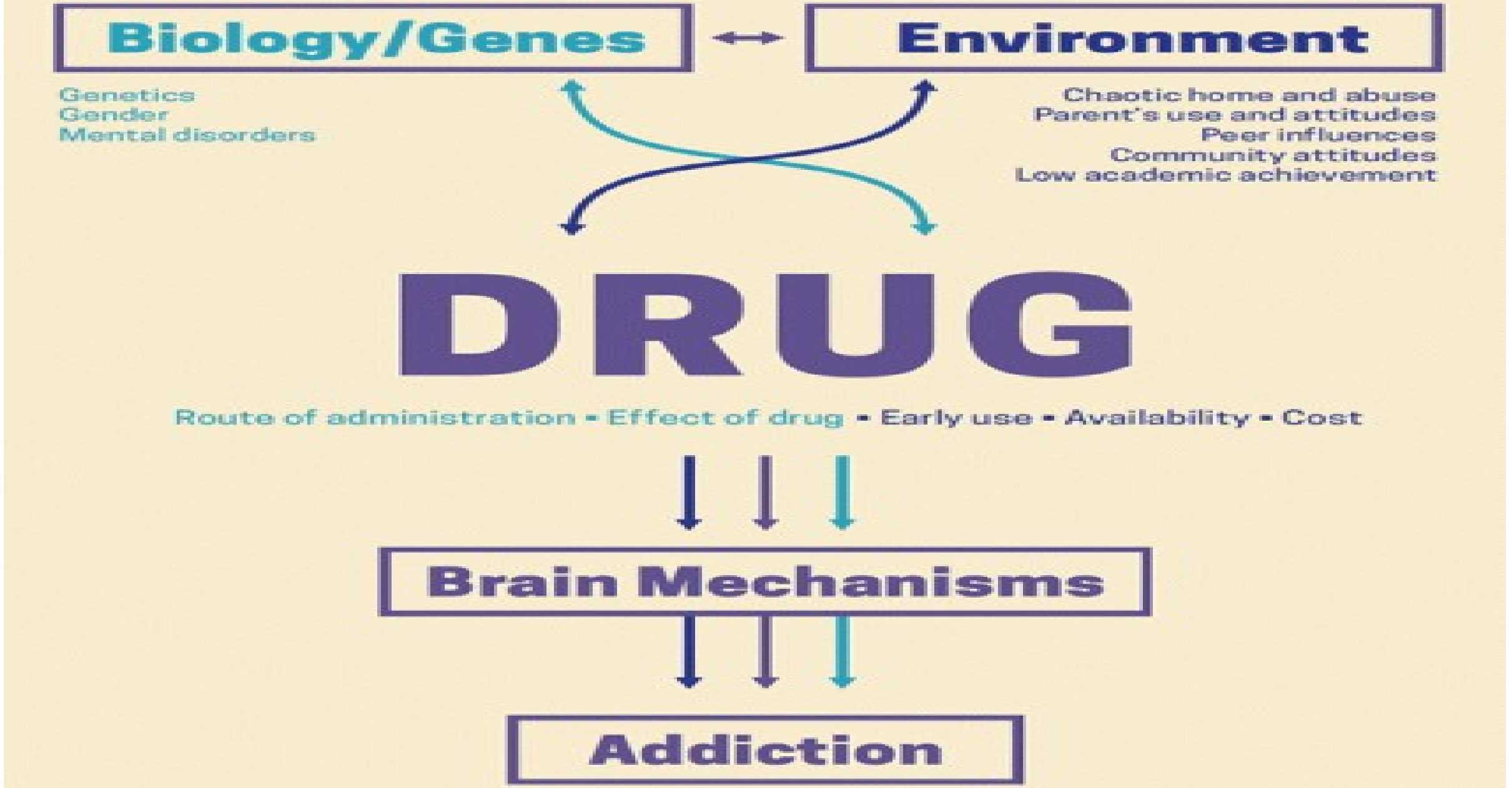
What is Drug Withdrawal?



What is Craving?

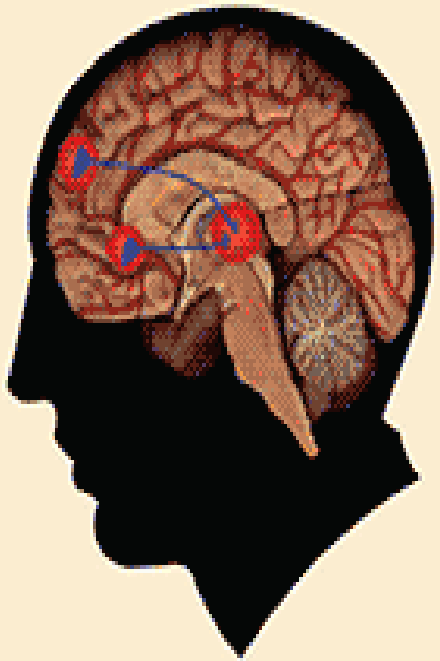


What does Loss of Control mean?


Biology/Genes
Environment
Genetics
Gender
Mental disorders
Chaotic home and abuse
Parent's use and attitudes
Peer influences
Community attitudes
Low academic achievement
DRUG
Route of administration • Effect of drug • Early use • Availability • Cost
Brain Mechanisms
Addiction

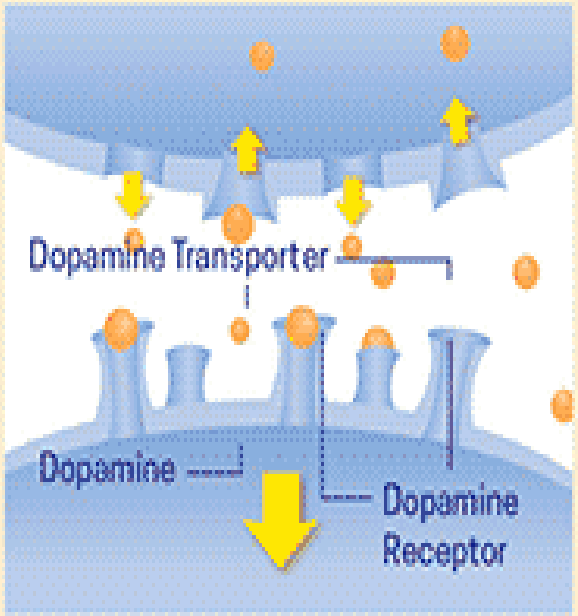
Some drugs target the brain's pleasure center

Brain reward (dopamine pathways)

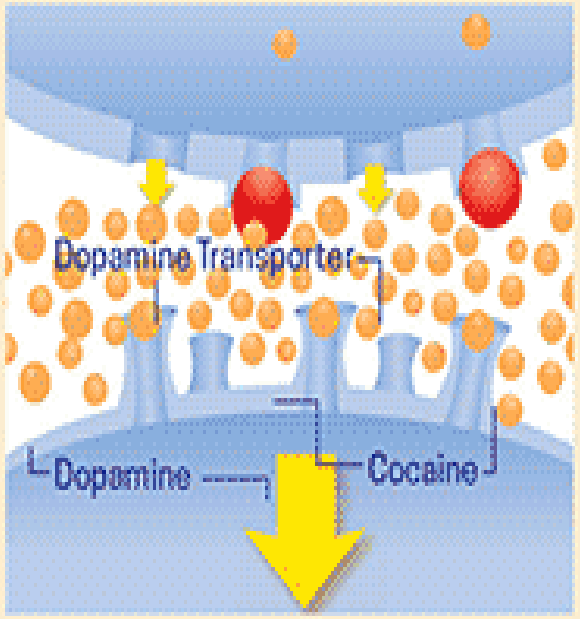


These brain circuits are important for natural rewards such as food, music, and sex.

How drugs can increase dopamine

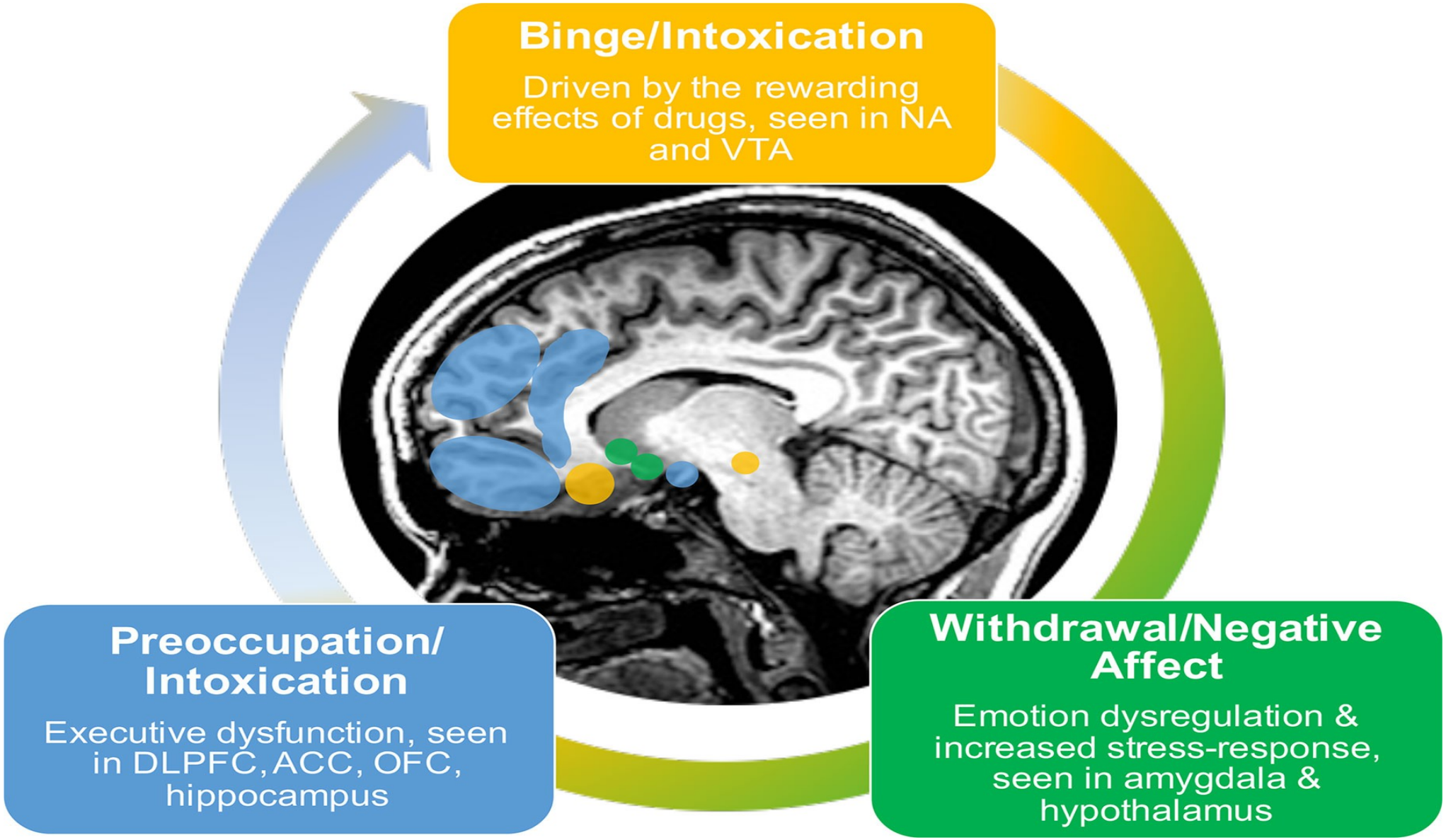


While eating food

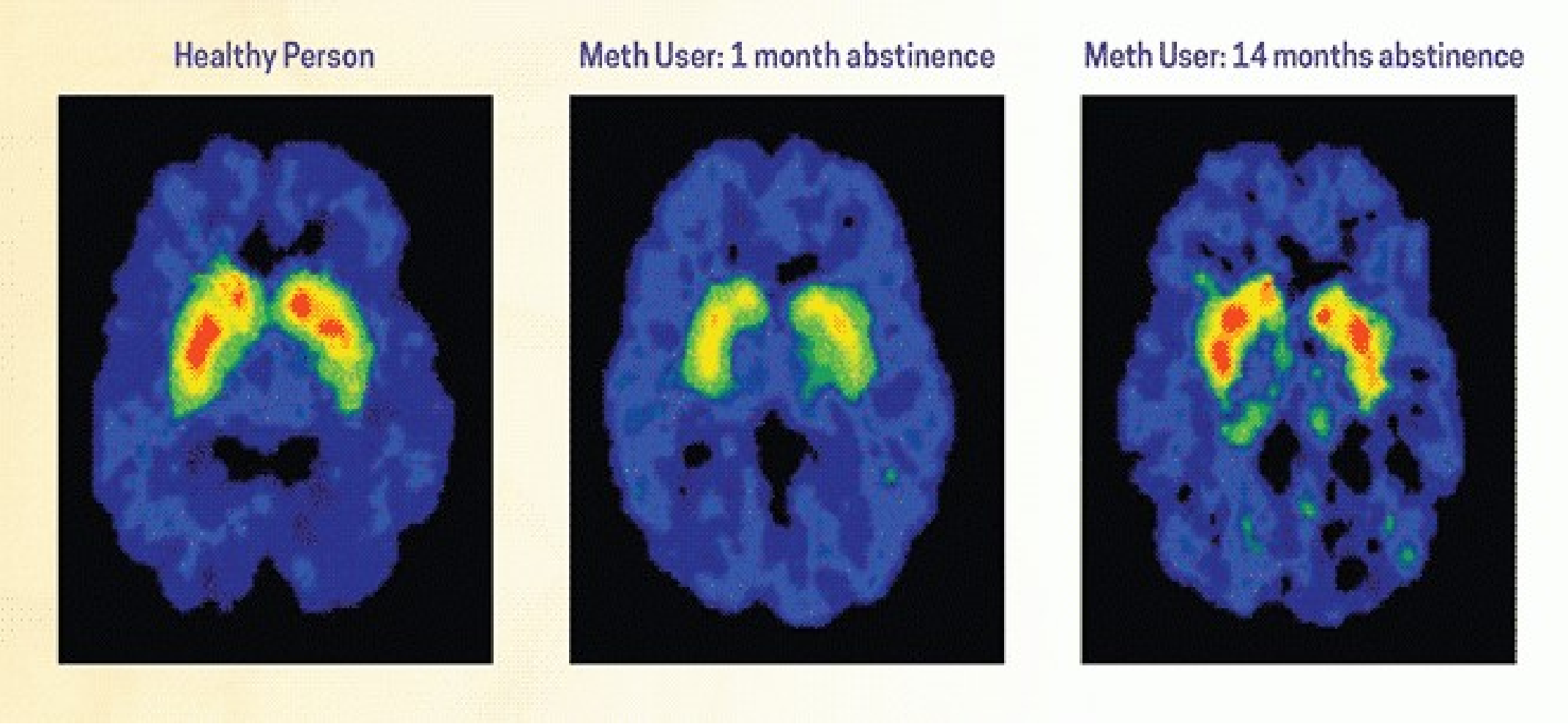


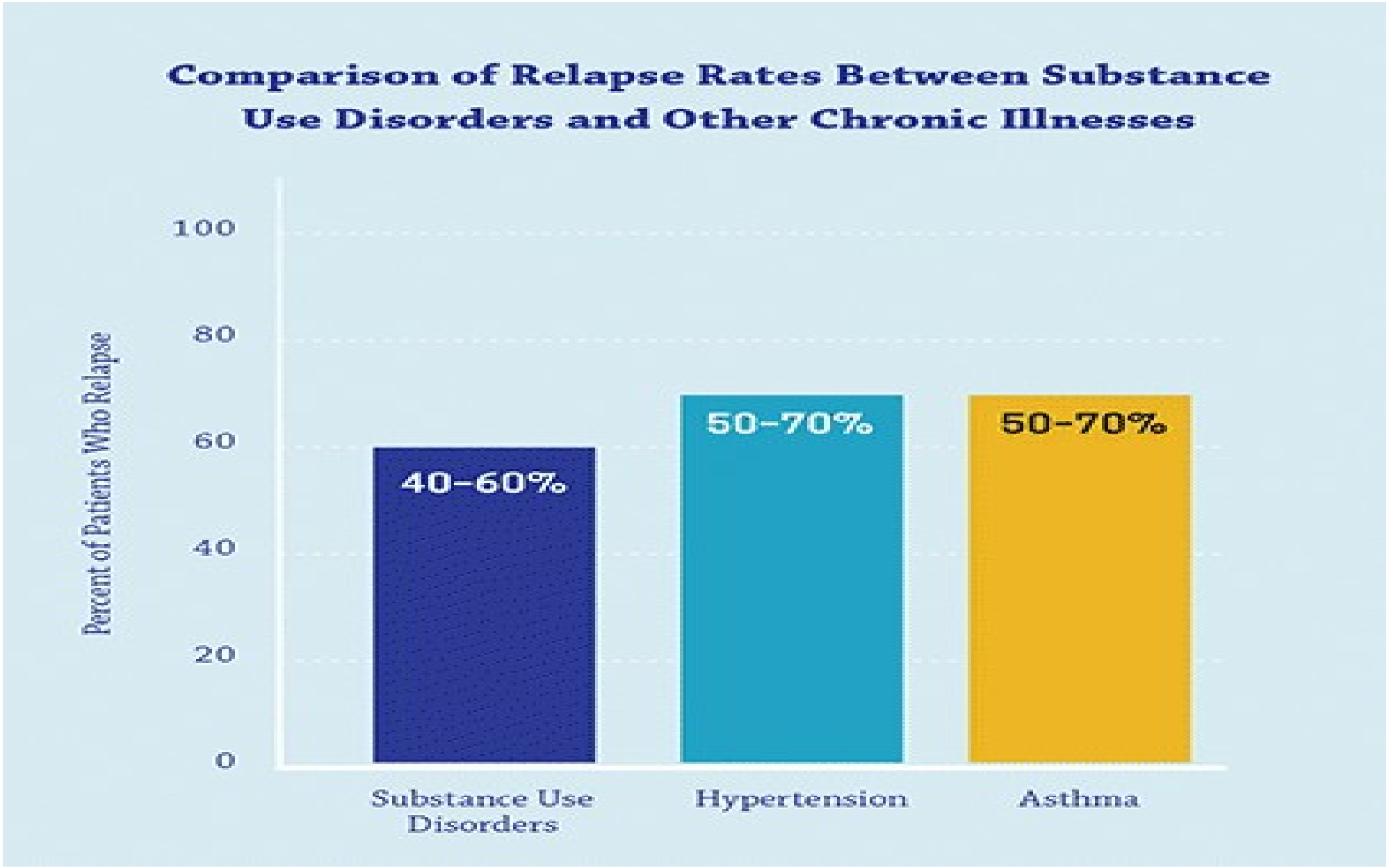
While using cocaine

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


Binge/Intoxication
Driven by the rewarding effects of drugs, seen in NA and VTA
Withdrawal/Negative Affect
Emotion dysregulation & increased stress-response, seen in amygdala & hypothalamus
Preoccupation/ Intoxication
Executive dysfunction, seen in DLPFC, ACC, OFC, hippocampus

How long does it take for the brain to recover after stopping the use of the substance?




Comparison of Relapse Rates Between Substance Use Disorders and Other Chronic Illnesses
Percent of Patients Who Relapse
100
80
60
40
20
0
40–60%
50–70%
50–70%
Substance Use Disorders
Hypertension
Asthma

Main Substances Causing Addiction

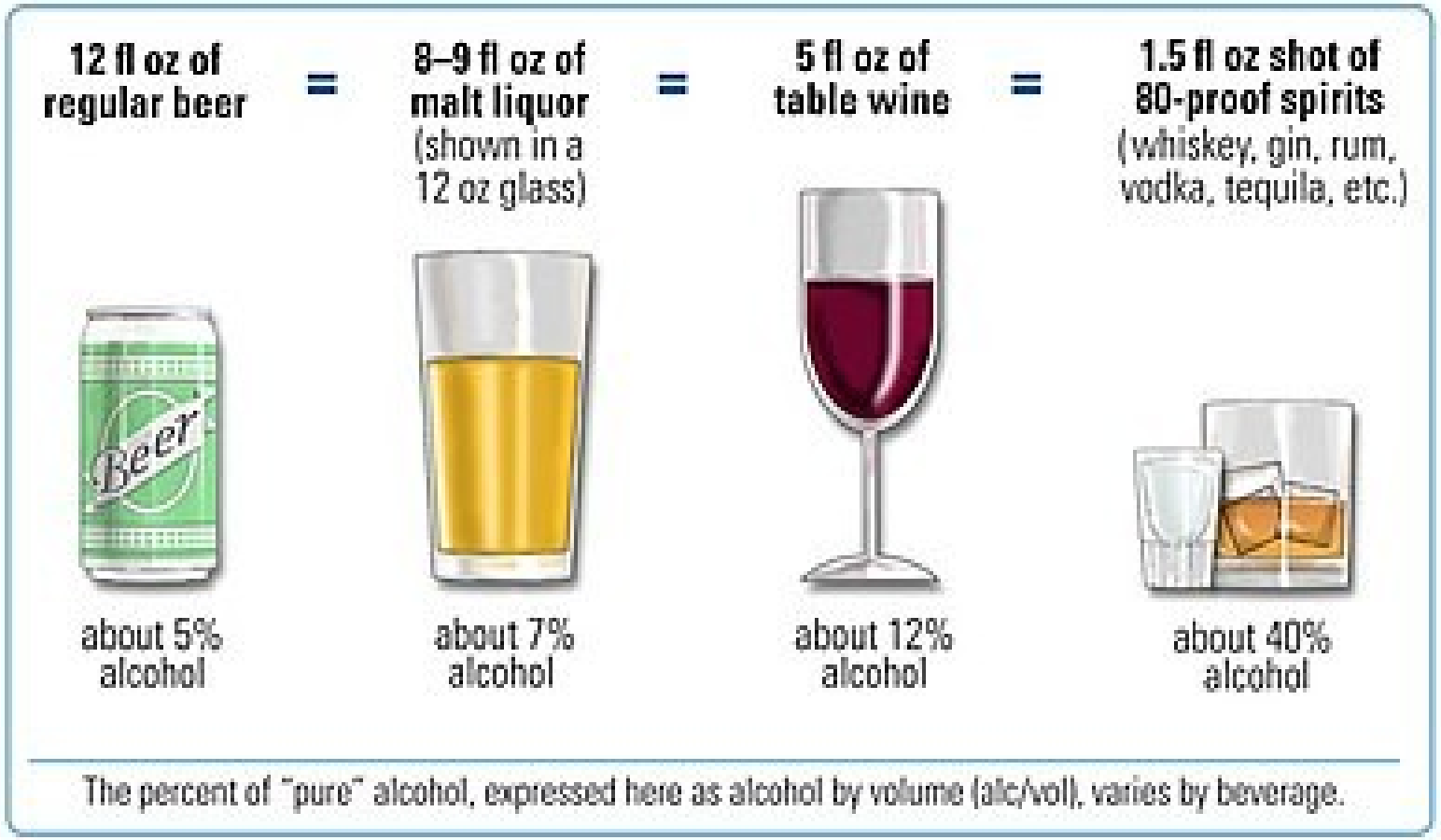
Alcohol

Opioids - Fentanyl

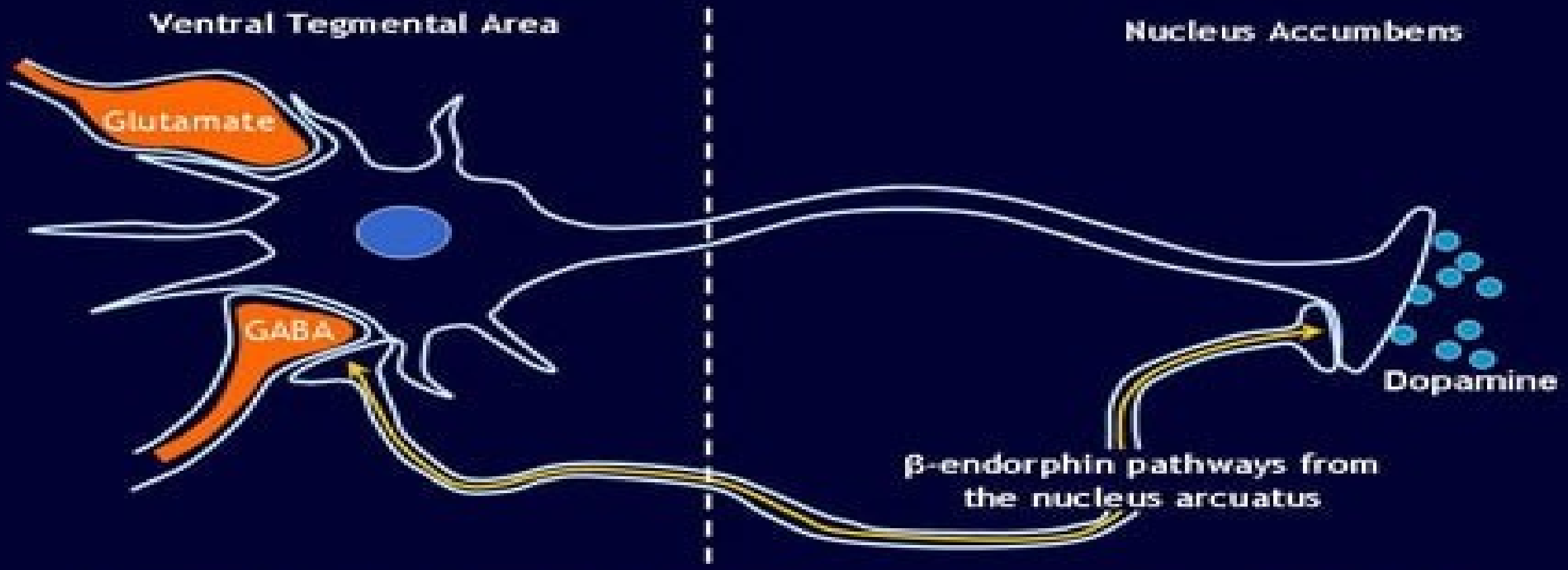
Methamphetamine

Alcohol

- Heavy drinking
  - 15 > drinks a week for men
  - 8 > drinks a week for women



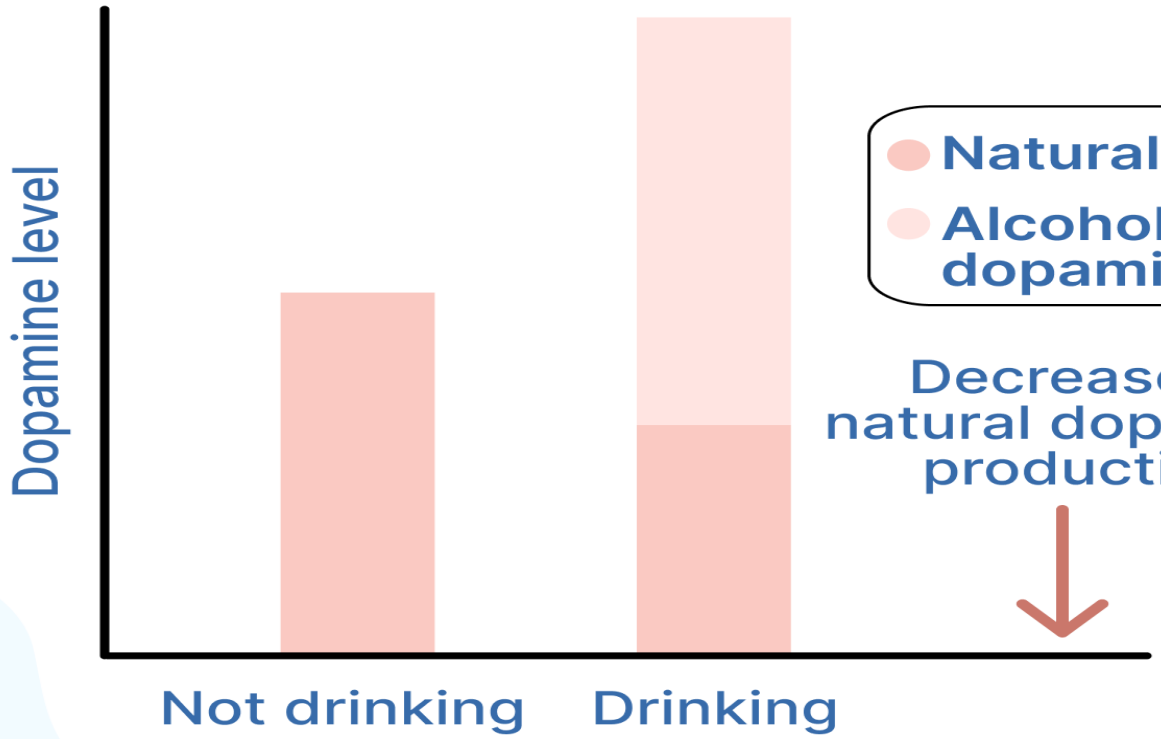
Alcohol Affects Diverse Neurotransmitter Systems



Alcohol releases opioid peptides that facilitate dopamine release

Adapted from Chao J, Nestler EJ. *Annu Rev Med.* 2004;55:113-132.

Dopamine and the Pleasure Principle



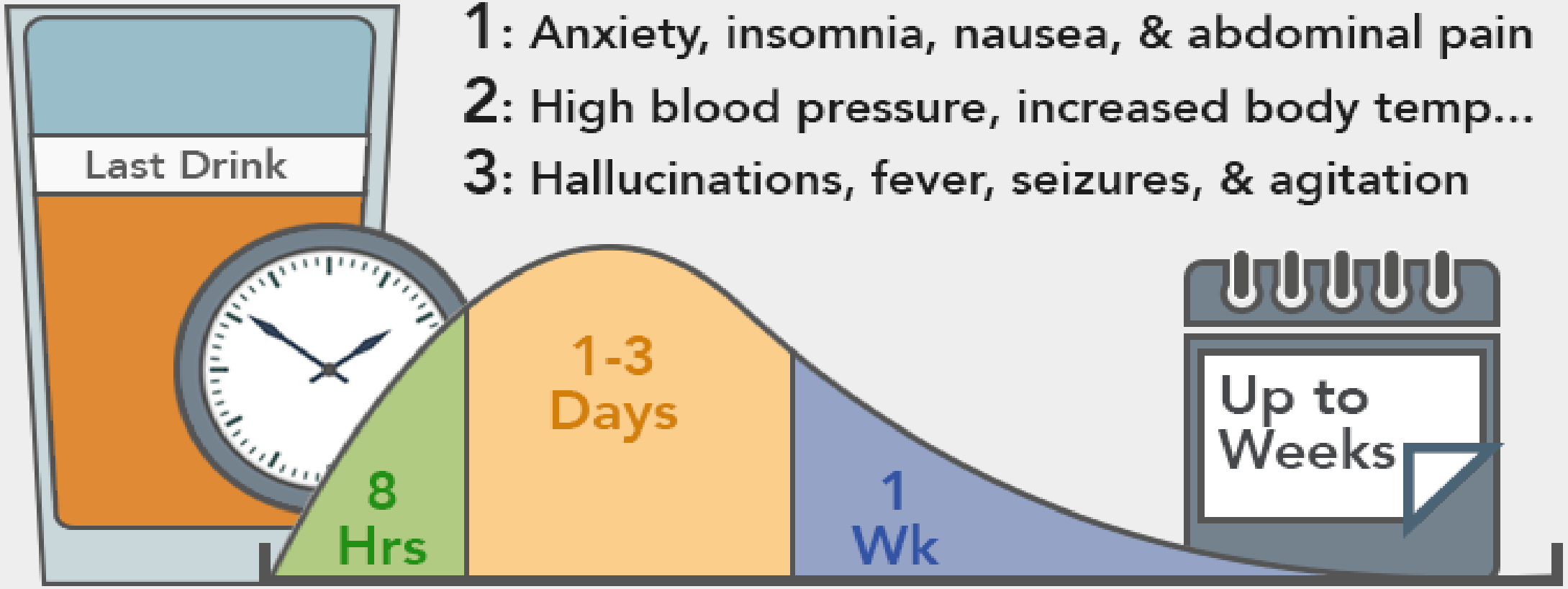
Tolerance in AUD

Blood Alcohol Level	Normal Brain	Addicted Brain
> .1*	Tipsy	Usually, no effect
> .2	Potentially on ventilator or in coma	Many times only minimal effect
> .3	Usually in coma or dead	Many times only moderate effect, but "functional"
.4 - .5	Barely alive	At times can function to a certain degree

Alcoholic - significantly greater tolerance

*.1 = 5 beers, 5 glasses of wine, 5 ozs. of Jack Daniels or any combination in 1 hour - based on a 150lb. male.

Alcohol Withdrawal Timeline



1: Anxiety, insomnia, nausea, & abdominal pain

2: High blood pressure, increased body temp...

3: Hallucinations, fever, seizures, & agitation

Kindling Effect of Repeated Alcohol Withdrawal

- Repeated episodes lead to an increased severity of the withdrawal syndrome.
- Neuronal adaptations from intoxication/withdrawal cycle accumulate.
- Increased neurotransmitter imbalances occur when alcohol is stopped.
- Chronic alcohol use and repeated withdrawal may lead to permanent alterations in GABA receptors.

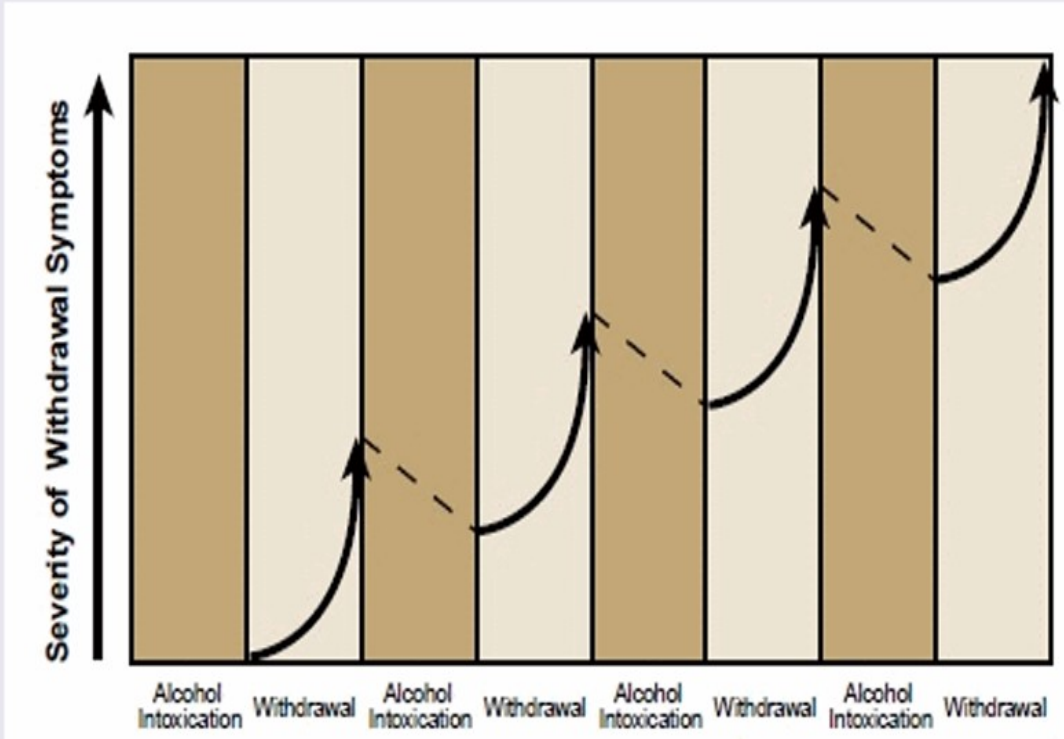
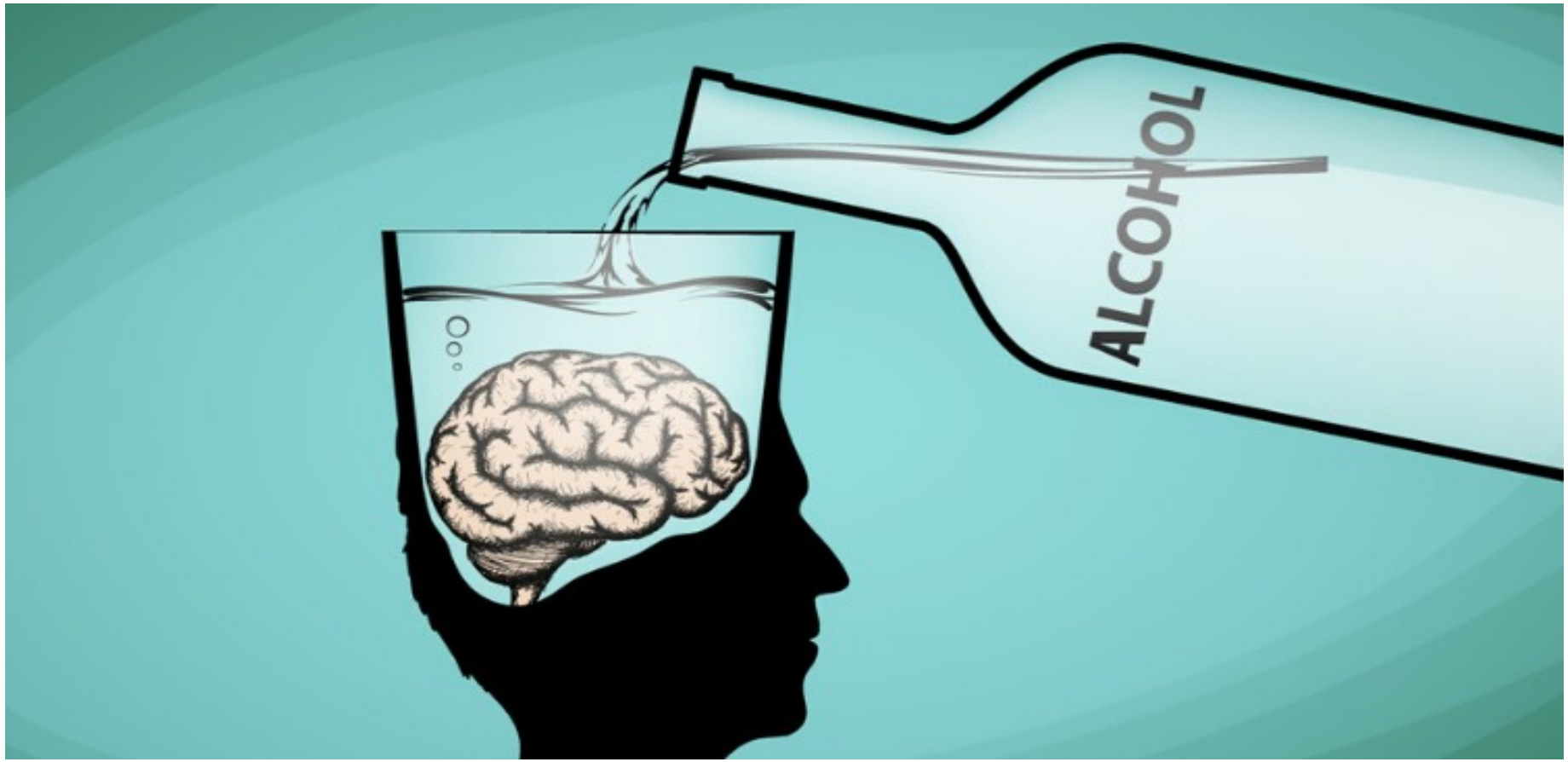


Figure 1 Graphic representation of the kindling concept during alcohol withdrawal. The term "kindling" refers to the phenomenon that people undergoing repeated cycles of intoxication followed by abstinence and withdrawal will experience increasingly severe withdrawal symptoms with each successive cycle.

Craving for Alcohol



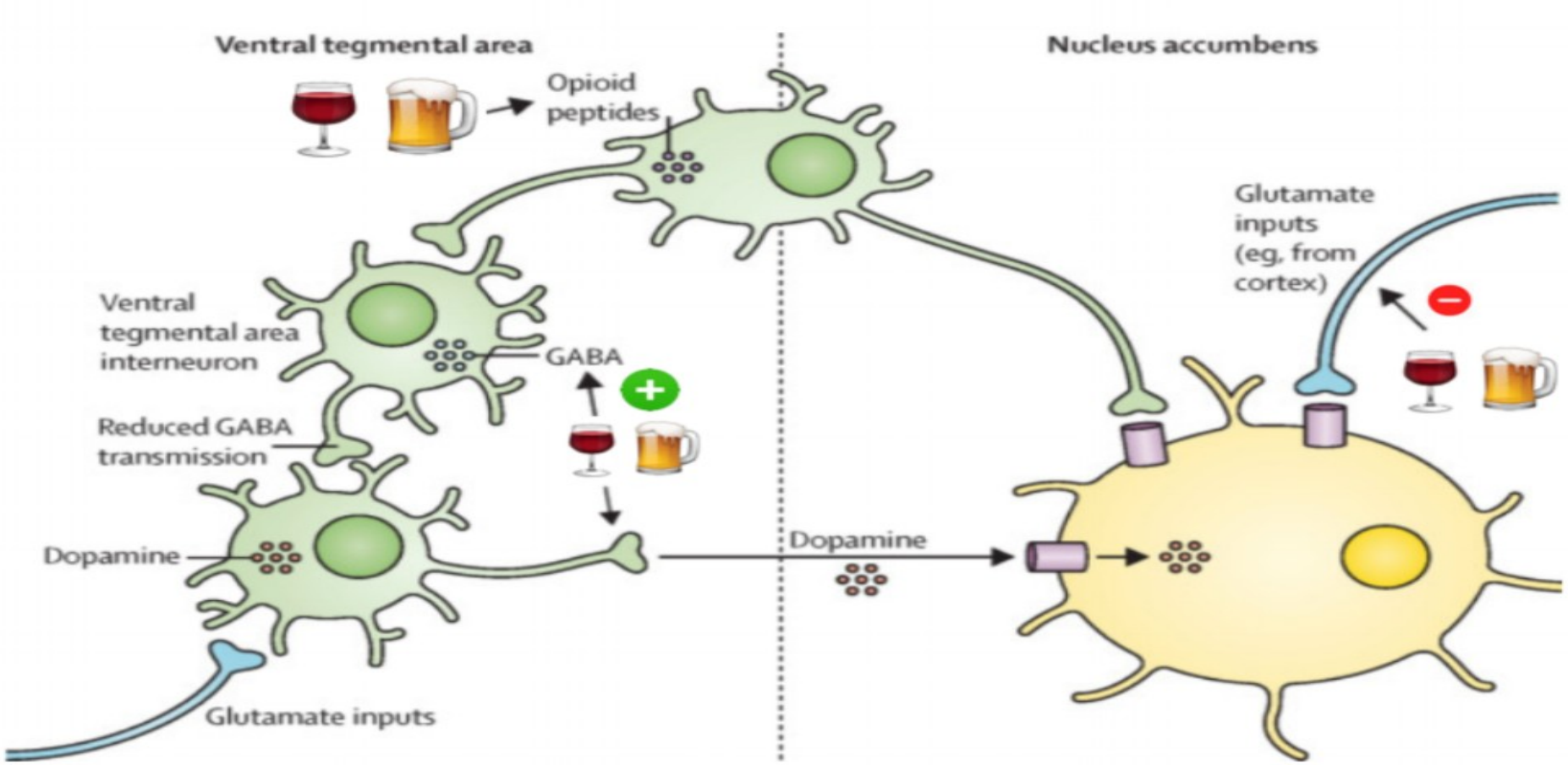
FDA-approved Pharmacological Treatments for Alcohol Dependence

1. Antabuse [package insert]. East Hanover, NJ: Odyssey Pharmaceuticals; 2001.
2. ReVia [package insert]. Pomona, NY: Duramed Pharmaceuticals, Inc.; 2005.
3. Campral [package insert] St. Louis, MO: Forest Pharmaceuticals; 2005.
4. Vivitrol [package insert]. Cambridge, MA: Alkermes, Inc.; 2006.

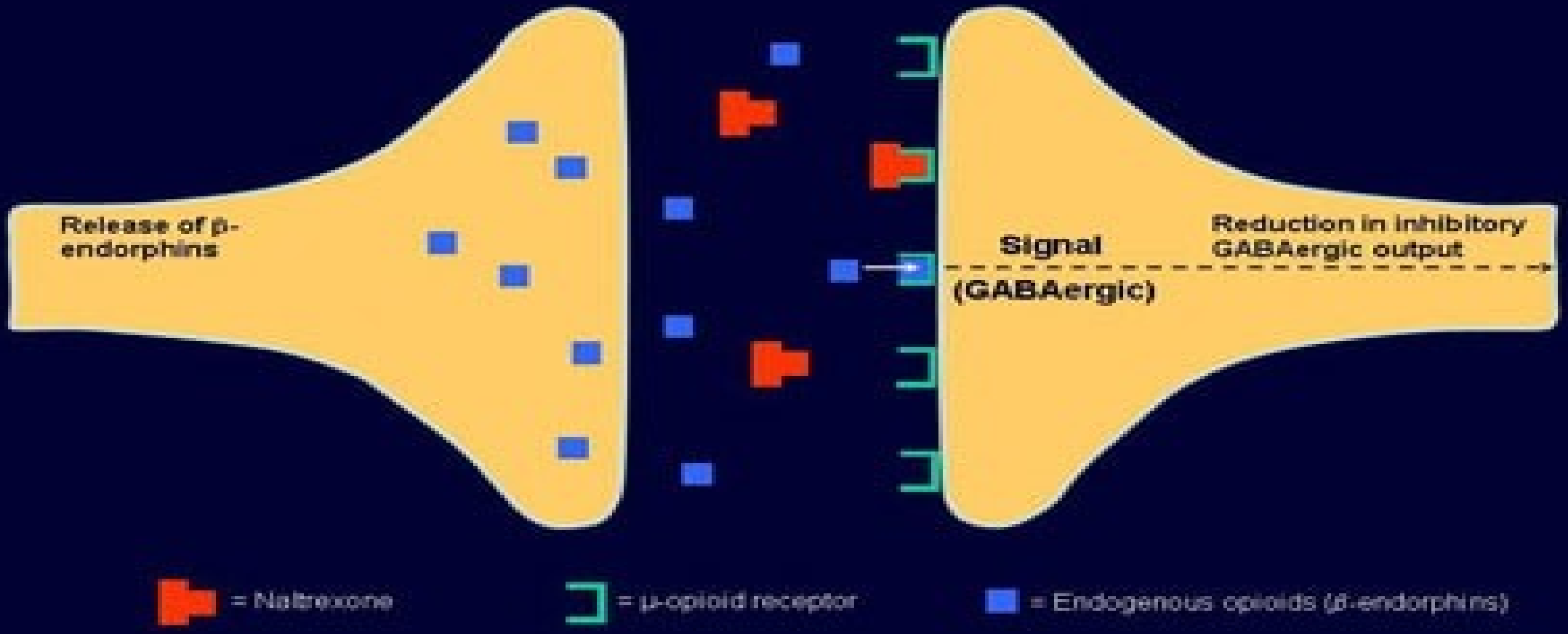
Medications to treat Alcohol Use Disorder

- Antabuse
  - Blocks the metabolism of alcohol – makes person sick
- Acamprosate
  - Promotes balance between the GABA and glutamate
- Naltrexone
  - Blocks the opioid receptors – preventing the buzz, decrease craving

Alcohol and opioid pathway in the brain

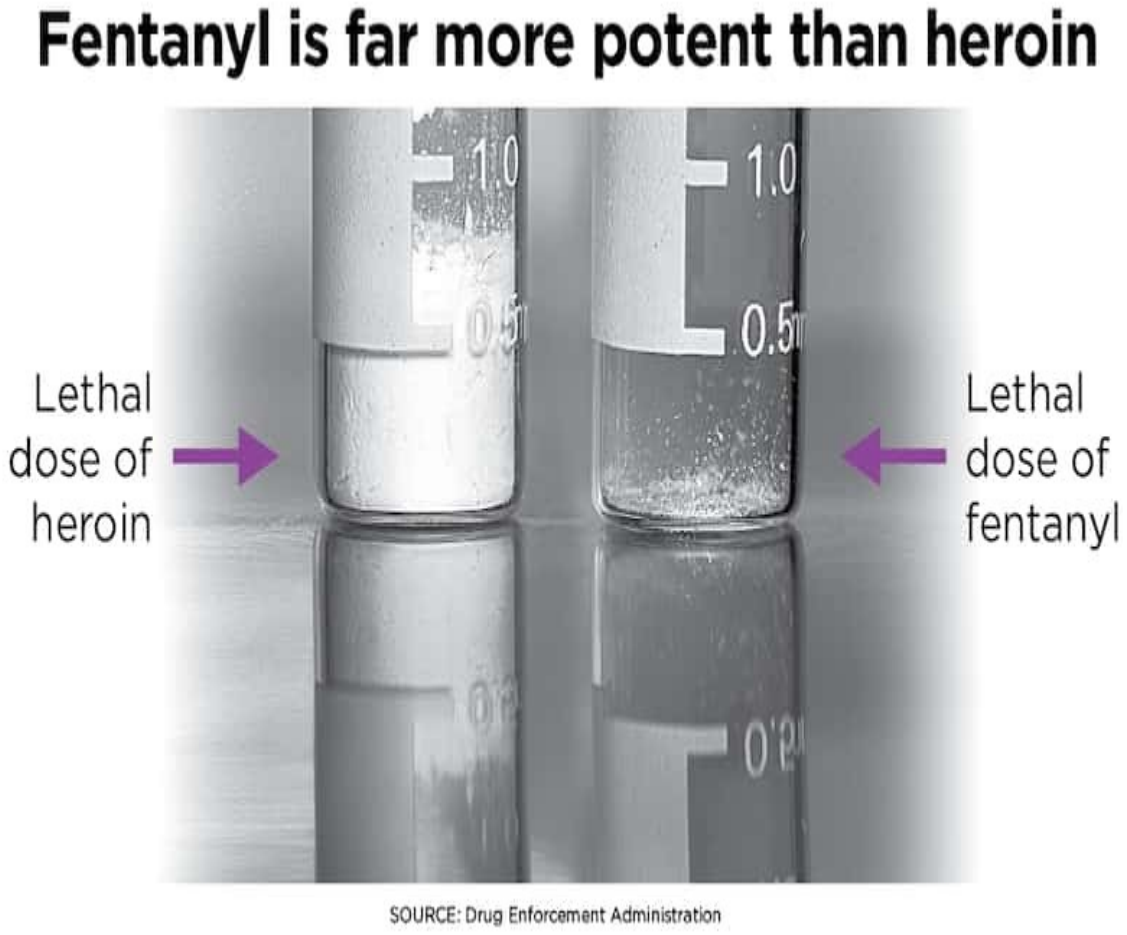


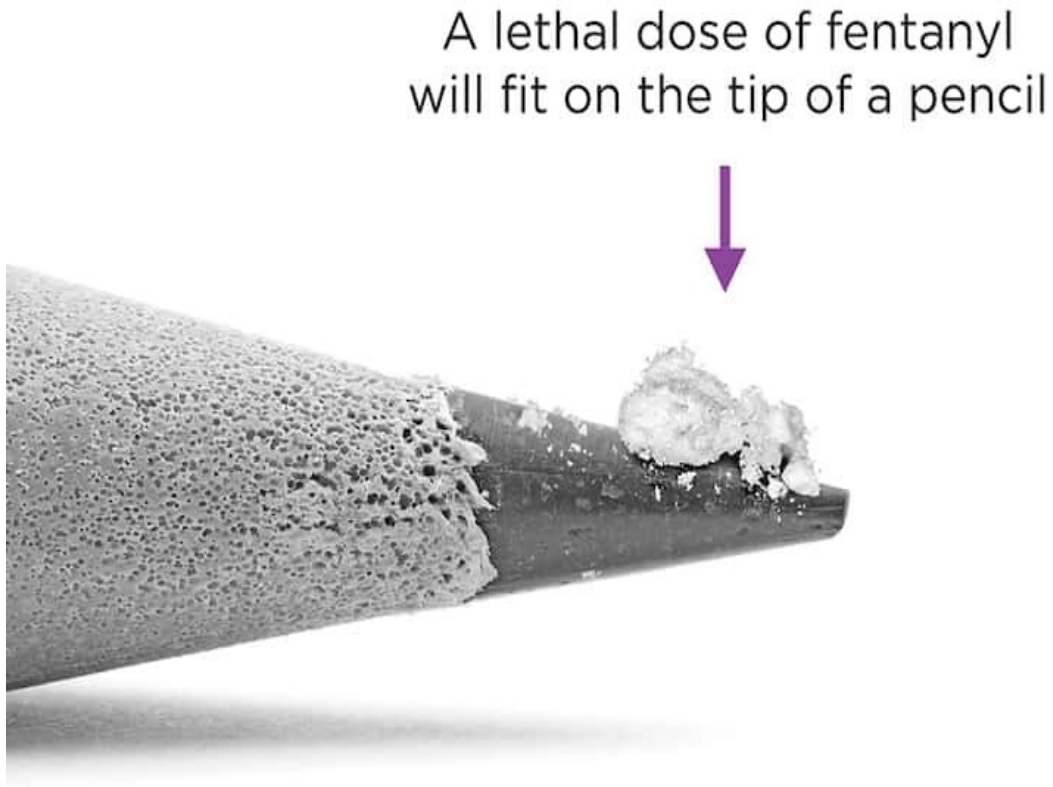
Naltrexone Modulates the Activity of Endogenous Opioids



Adapted from Kenna GA et al. *Am J Health Syst Pharm*. 2004;61:2272-2279.

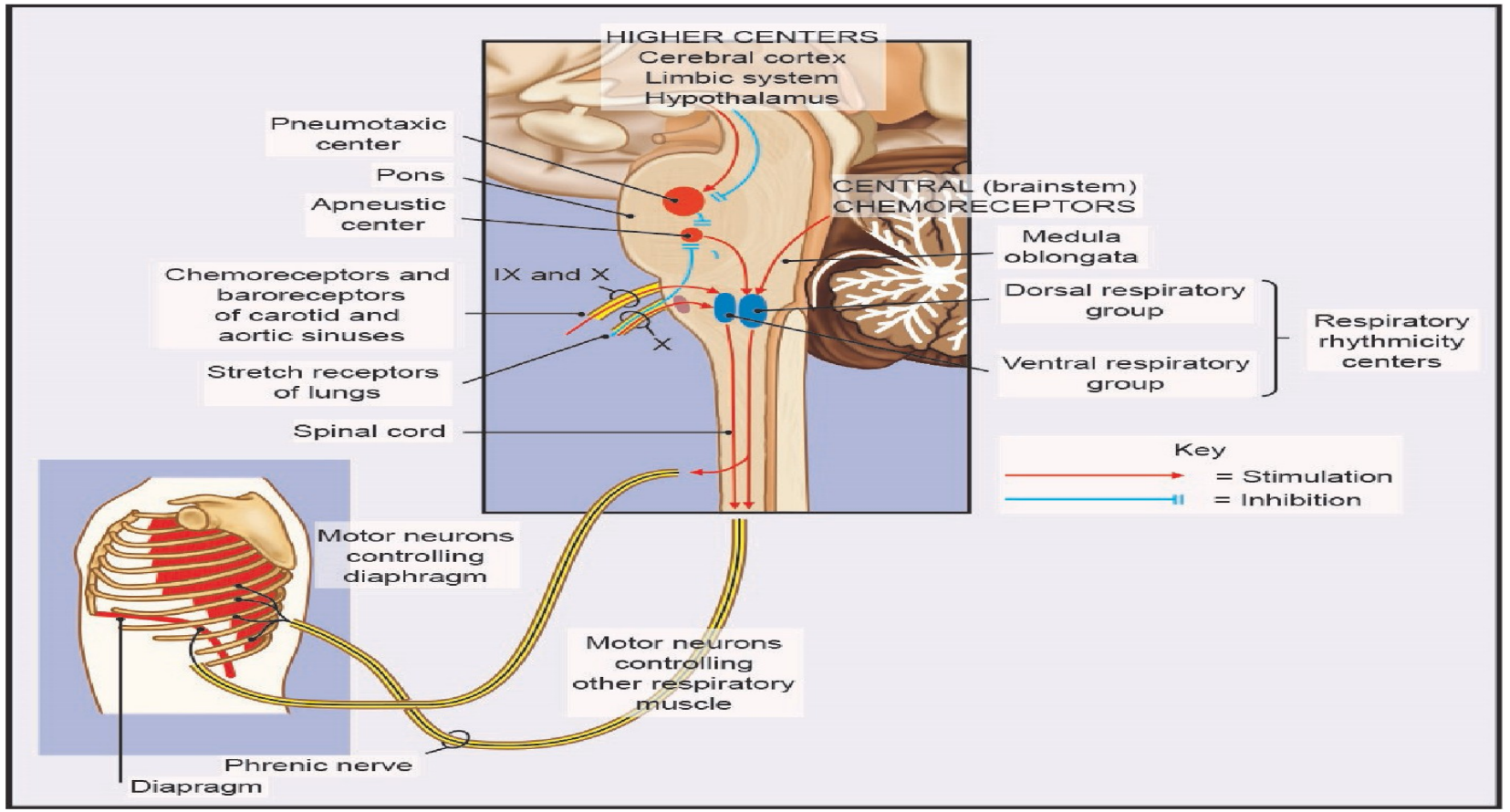
Opioids

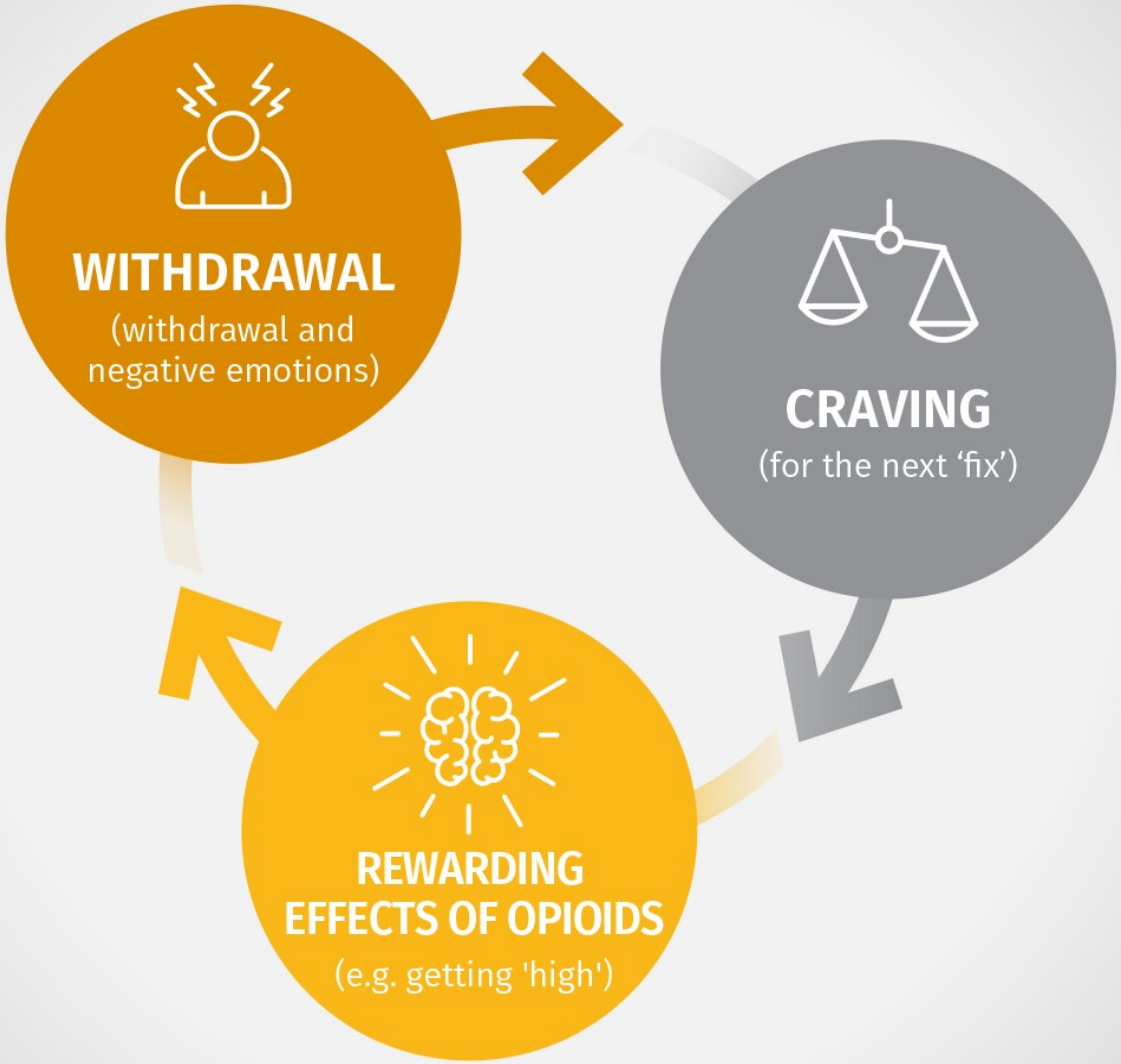

Fentanyl is far more potent than heroin
Lethal dose of heroin
Lethal dose of fentanyl
1.0
0.5
1.0
0.5
SOURCE: Drug Enforcement Administration

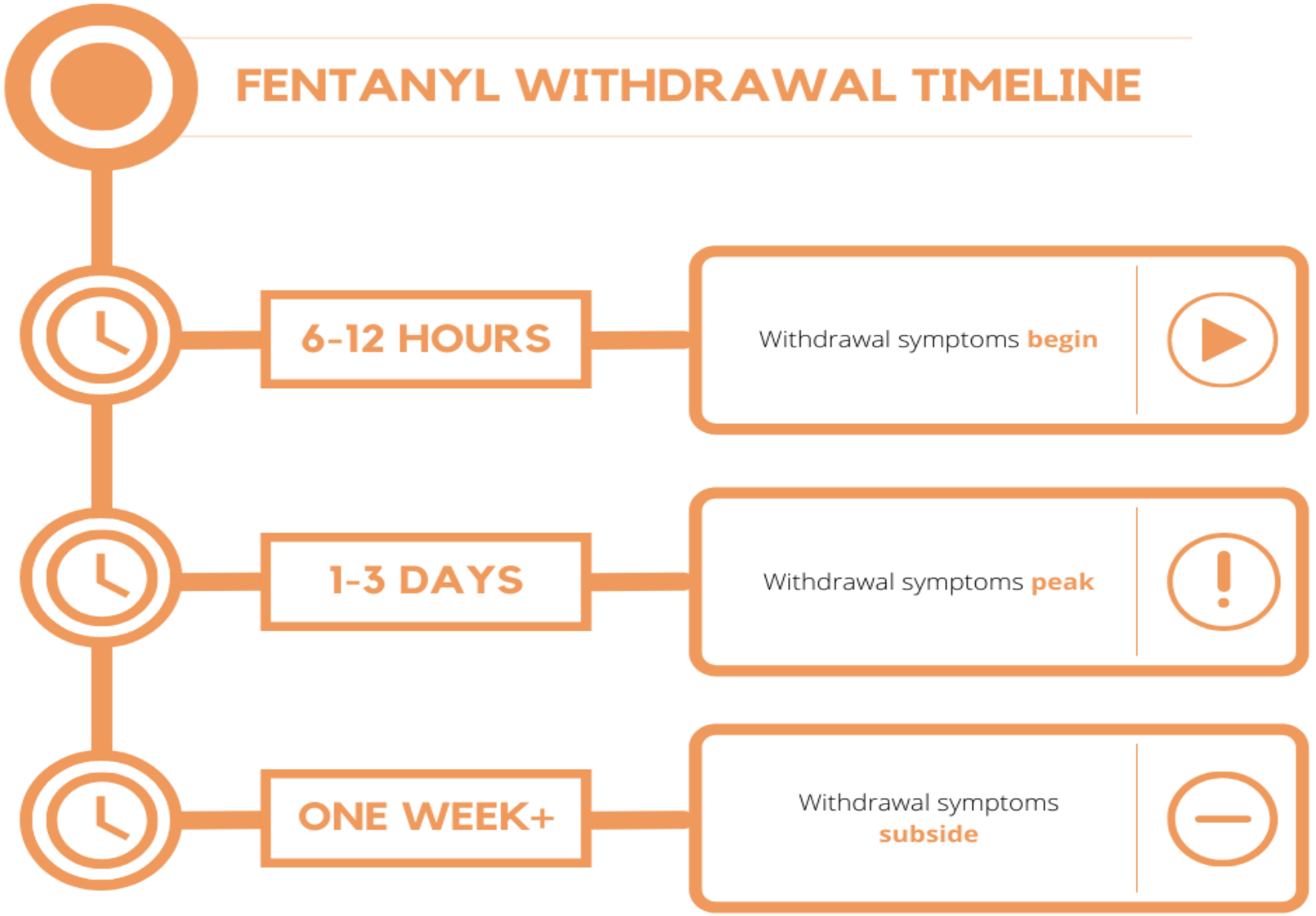

A lethal dose of fentanyl will fit on the tip of a pencil

Cause of death in Opioid Overdose

Figure 1. Simple schematic representation of the ventilatory control system



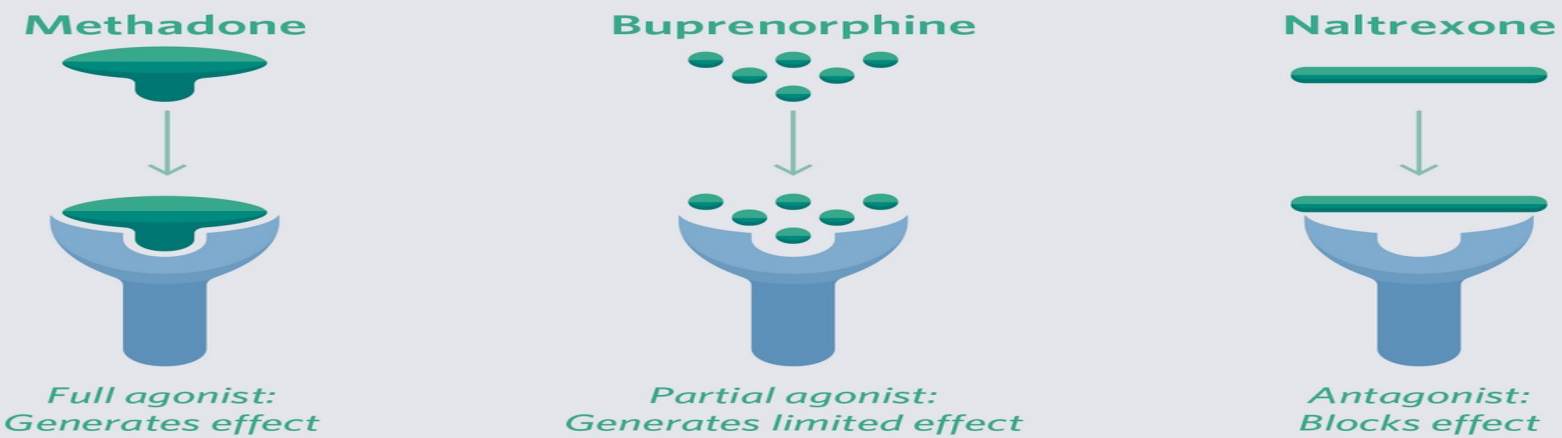

WITHDRAWAL
(withdrawal and negative emotions)
CRAVING
(for the next ‘fix’)
REWARDING EFFECTS OF OPIOIDS
(e.g. getting 'high')



Physical withdrawal symptoms subside, but psychological withdrawal symptoms persists for months to years.

Figure 1

How OUD Medications Work in the Brain



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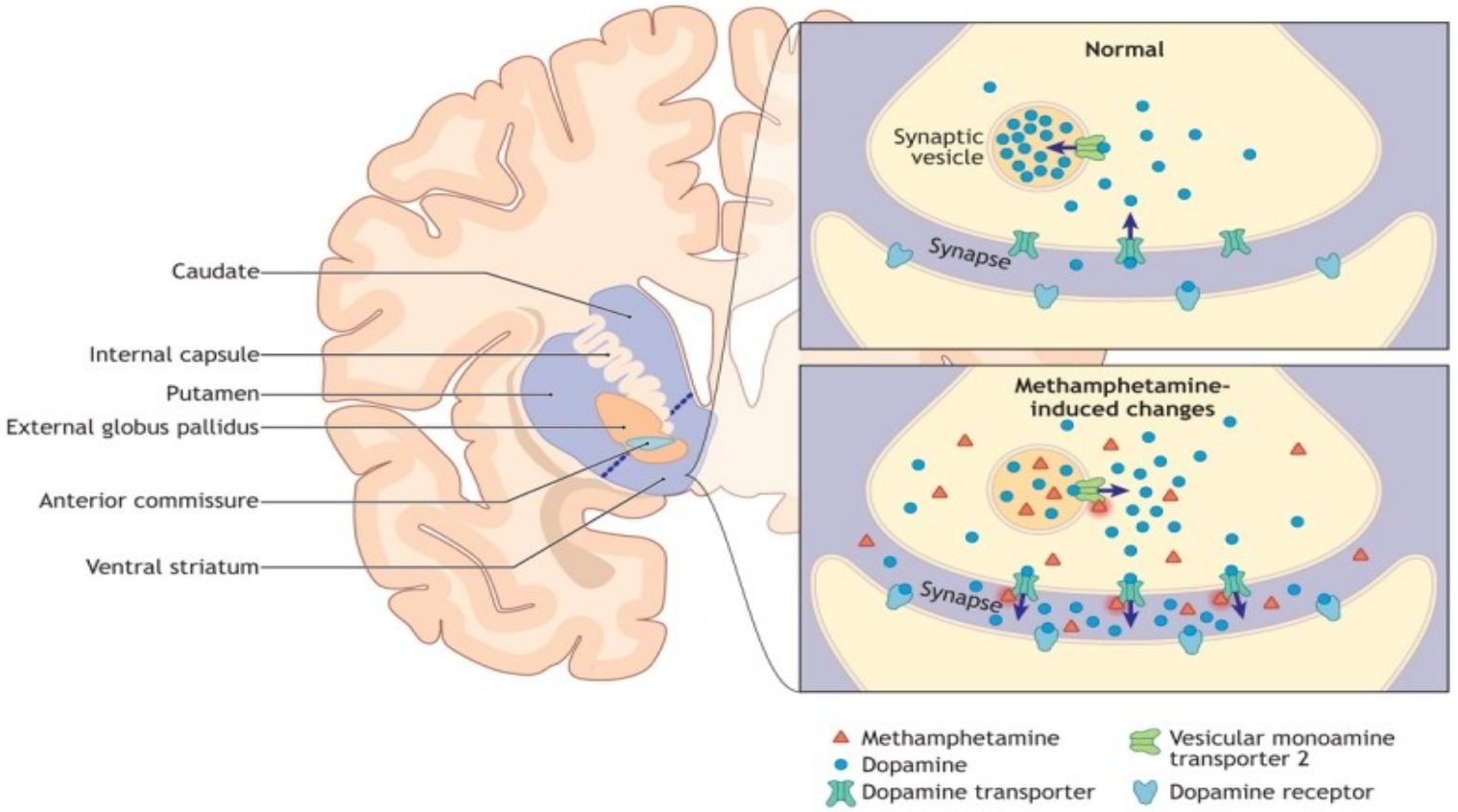
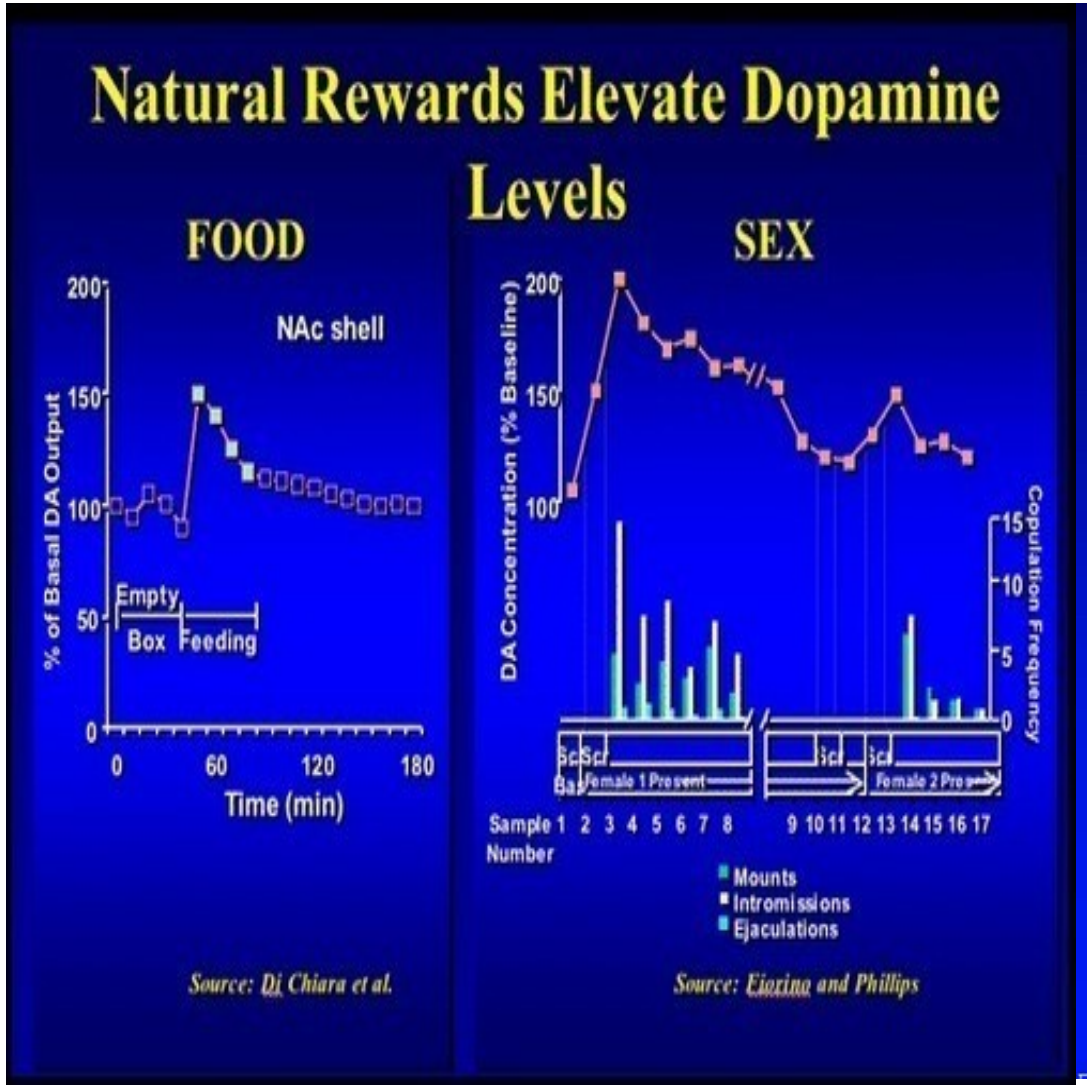
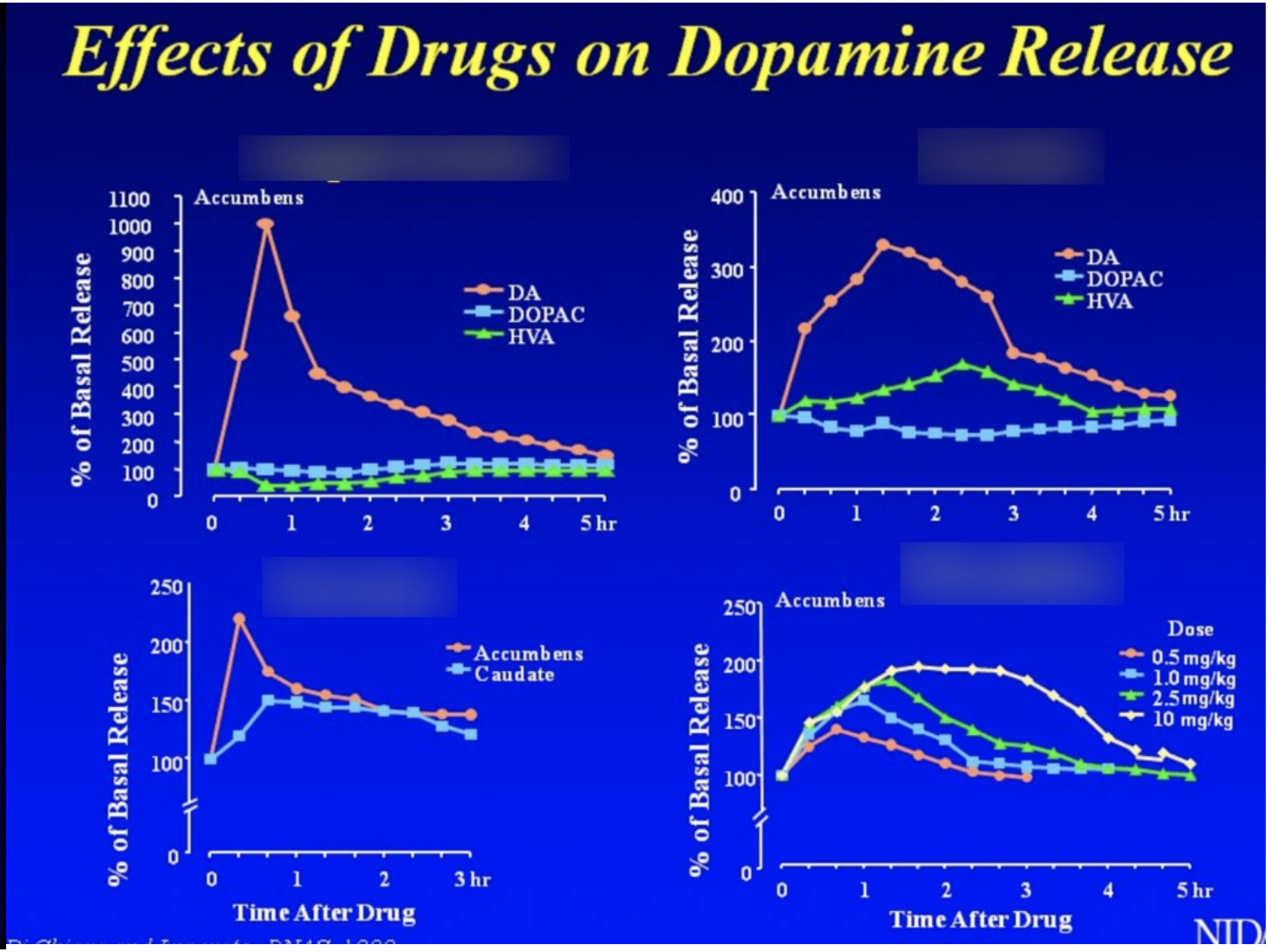
Methamphetamine

Mechanism of action of Meth



Release of dopamine, serotonin and norepinephrine into synapses

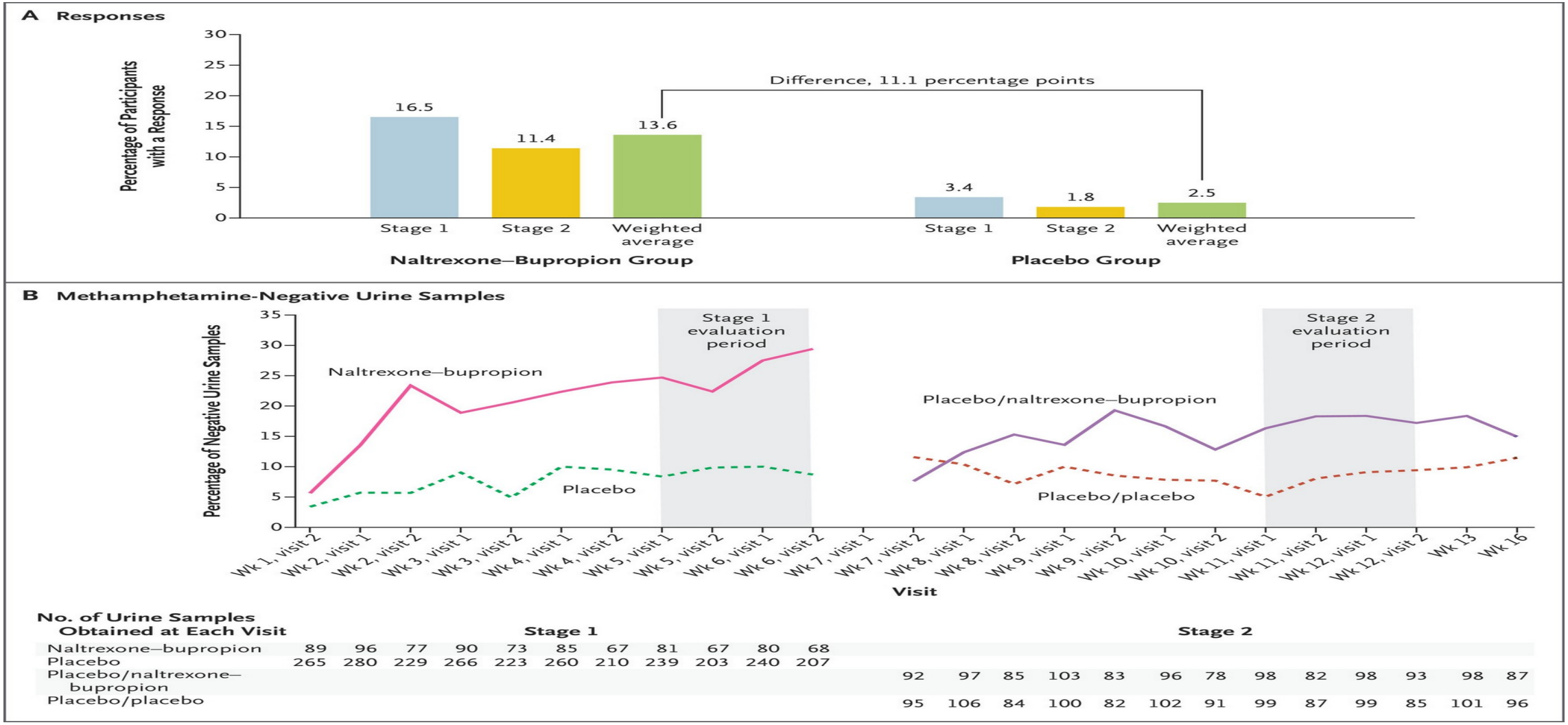

Natural Rewards Elevate Dopamine Levels
FOOD
NAc shell
% of Basal DA Output
200
150
100
50
0
Empty
Box
Feeding
0
60
120
180
Time (min)
Source: Di Chiara et al.
SEX
DA Concentration (% Baseline)
200
150
100
Copulation Frequency
15
10
5
0
Female 1 Present
Female 2 Present
Sample Number
1 2 3 4 5 6 7 8
9 10 11 12 13 14 15 16 17
Mounts
Intromissions
Ejaculations
Source: Fiorino and Phillips


Effects of Drugs on Dopamine Release
Accumbens
% of Basal Release
1100
1000
900
800
700
600
500
400
300
200
100
0
DA
DOPAC
HVA
0
1
2
3
4
5 hr
Accumbens
% of Basal Release
400
300
200
100
0
DA
DOPAC
HVA
0
1
2
3
4
5 hr
% of Basal Release
250
200
150
100
0
Accumbens
Caudate
0
1
2
3 hr
Time After Drug
Accumbens
% of Basal Release
250
200
150
100
0
Dose
0.5 mg/kg
1.0 mg/kg
2.5 mg/kg
10 mg/kg
0
1
2
3
4
5 hr
Time After Drug

Bupropion and Naltrexone in Methamphetamine Use Disorder

Madhukar H. Trivedi, M.D., Robrina Walker, Ph.D., Walter Ling, M.D.,

NEJM 2021



No. of Urine Samples Obtained at Each Visit	Stage 1											Stage 2											
Naltrexone–bupropion	89	96	77	90	73	85	67	81	67	80	68												
Placebo	265	280	229	266	223	260	210	239	203	240	207												
Placebo/naltrexone–bupropion												92	97	85	103	83	96	78	98	82	98	93	98	87
Placebo/placebo												95	106	84	100	82	102	91	99	87	99	85	101	96

Naltrexone/Bupropion Effectiveness Found Comparable to Other Substance Use Pharmacotherapies

With an estimated number needed to treat of 9, naltrexone/bupropion is similarly effective at reducing methamphetamine use as other substance use or pain medications that are approved by the FDA.

Name of medication	Number Needed to Treat
Naltrexone/bupropion for methamphetamine use disorder	1 in 9
Varenicline for smoking cessation	1 in 11
Acomprosate for alcohol use disorder	1 in 9
NSAIDS for back pain	1 in 14
High-dose buprenorphine for opioid use disorder	1 in 2

Source: Naltrexone/bupropion number needed to treat (NNT) estimated from M. H. Trivedi, et al., *NEJM,* January 14, 2021. Remaining NNT data taken from Cochrane Reviews of the medications (https://www.cochranelibrary.com/).

Psychotherapeutic/Behavioral interventions

Identification of Practices Associated with Treatment of Stimulant Use Disorders

Motivational Interviewing

Goal

Motivational interviewing (MI) is a treatment approach that helps individuals overcome ambivalent feelings and insecurities. In the process, individuals become motivated to change their behavior and reduce or stop their stimulant use.

Developers of motivational interviewing define it as "a directive, client-centered counselling style for eliciting behavior change by helping clients explore and resolve ambivalence."[2]

OUTCOMES ASSOCIATED WITH MOTIVATIONAL INTERVIEWING

Studies included in this evidence review demonstrated that use of MI for people with stimulant use disorders was associated with reductions in:

- Number of days of stimulant use
- Amount of stimulant used per day

All outcomes were measured using either urine toxicology or participant self-report. The time between treatment and follow-up varied from zero months (immediately post-treatment) to six months.

Contingency Management

Strong Evidence

Goal

Contingency management (CM) is a type of behavioral therapy grounded in the principles of operant conditioning. Operant conditioning is a method of learning in which desired behaviors are reinforced with prizes, privileges, or cash.

For treatment of stimulant use disorders, incentivized behaviors might include:

- Attendance at treatment sessions
- Adherence to prescribed medications for other health conditions
- Provision of stimulant-negative urine specimens

OUTCOMES ASSOCIATED WITH CONTINGENCY MANAGEMENT

Studies included in this evidence review demonstrated that use of CM for people with stimulant use disorders was associated with reductions in:

- Number of days of stimulant use
- Stimulant cravings
- New stimulant use
- HIV risk behaviors

All outcomes were measured using either urine toxicology, participant self-report, or the Addiction Severity Index Scale.[11] The time between treatment and follow-up varied from zero months (immediately post-treatment) to nine months.

The Benefits of

PEER SUPPORT

in Substance Abuse Recovery

VIRTUE

In Summary

- Addiction changes the brain circuitry.
- Addiction is a chronic brain disorder.
- Relapses are common like other chronic disorders.
- Medications are underutilized.
- Meds + therapy + peer support