

Opioid Curriculum: Tertiary Prevention

SUBSTANCE USE DISORDER

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Learning Objectives

By the end of this lecture students will be able to:

- Understand how opioid analgesics differ from other analgesics.
- Explain how opioid use disorder (OUD) is similar to other substance use disorders
- List the DSM-5 criteria for OUD.
- Understand the molecular mechanisms that dictate the epigenetics of addiction.
- Differentiate two clinical models of addiction.
- Identify risk factors for developing OUD.



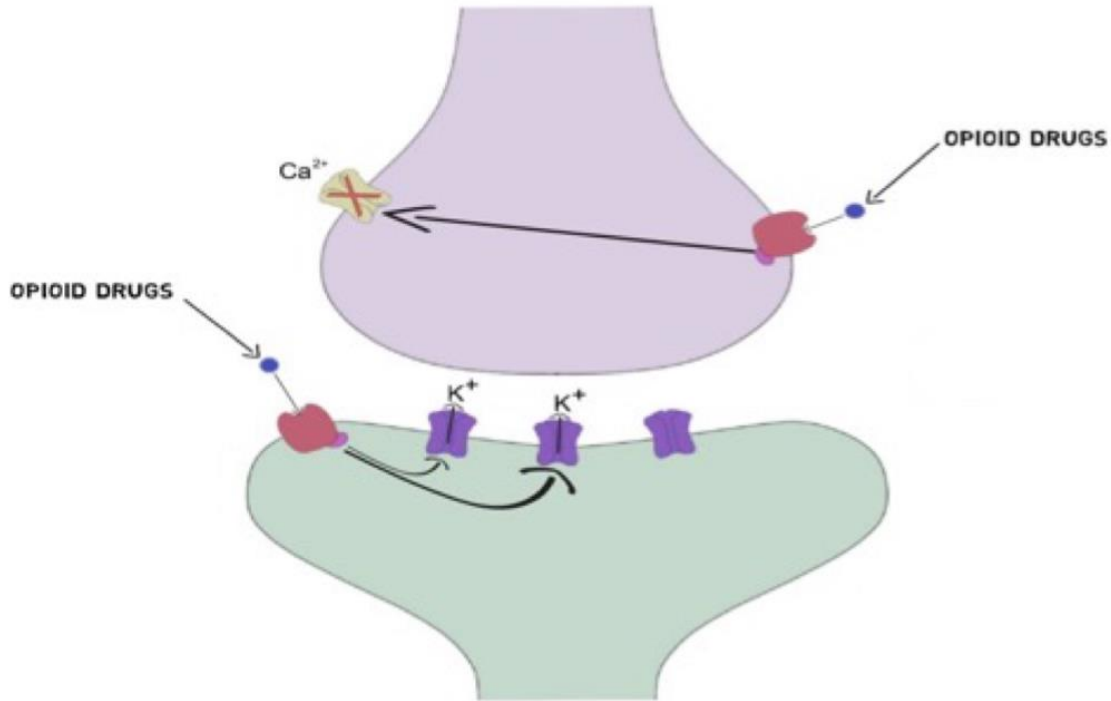
OPIOID ANALGESIA

Why do patients like opioids?

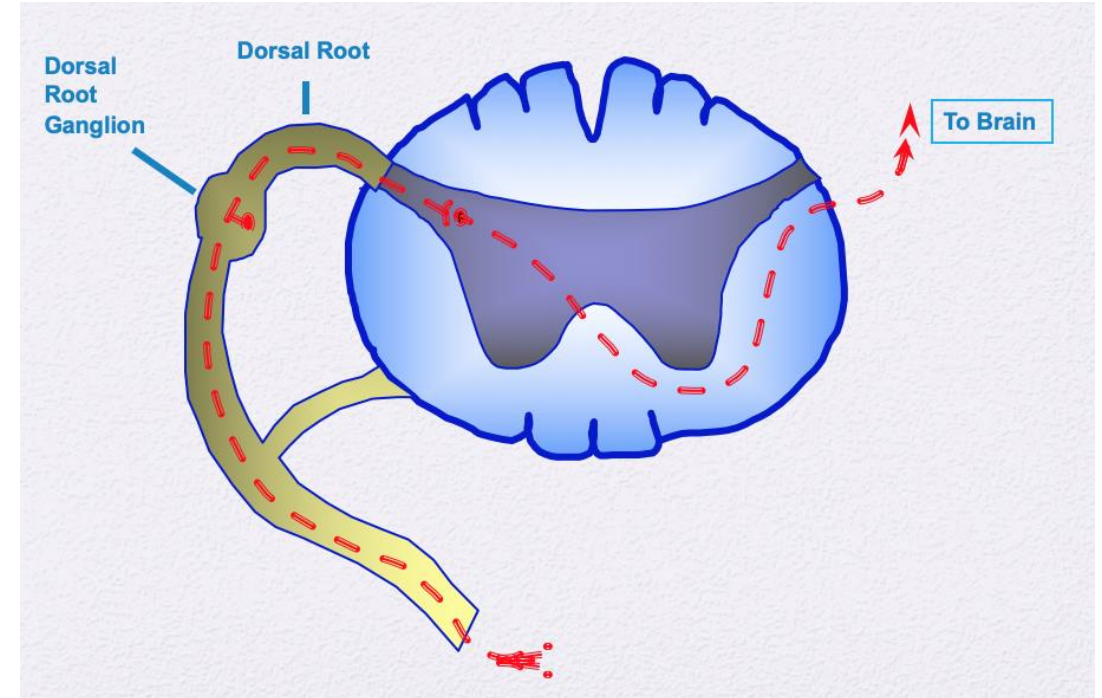


Opioids Act on Different Levels

Molecular:



Anatomic:

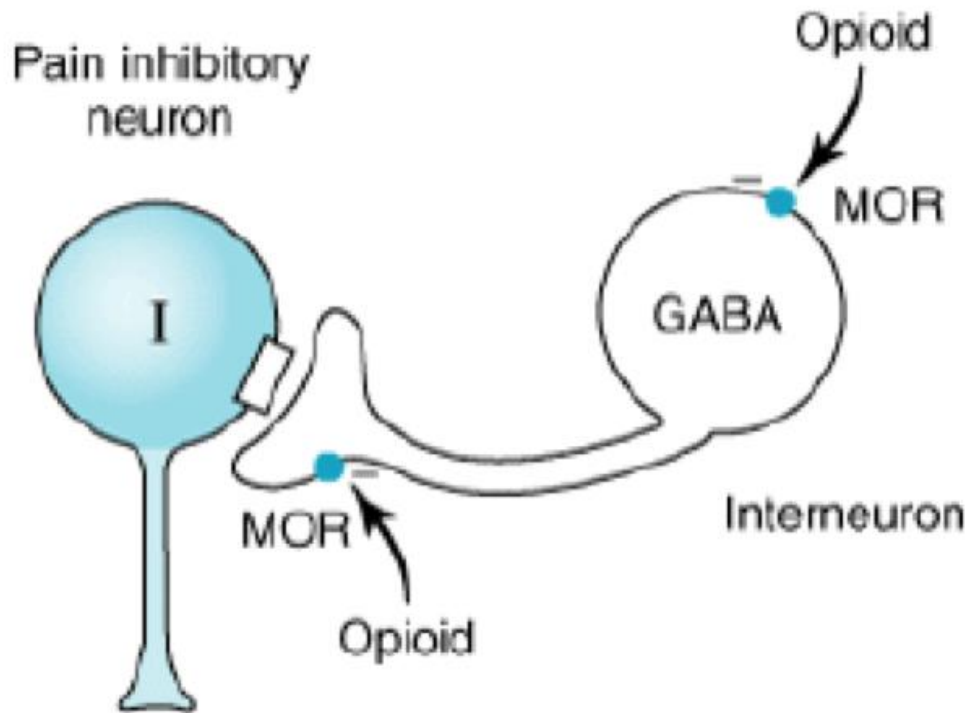


Pre-synaptic - $\downarrow Ca^{++} = \downarrow NT$ release
Post-synaptic - $\uparrow K^{+} = \uparrow$ Stability

Peripheral nociceptors (Dorsal horn)
Substantia Gelatinosa
Spinal cord and brain



Unique Quality of Mu Opioid Receptors



- Inhibit GABA in the PAG
- Stop inhibition of descending pathways

Pain Pathways

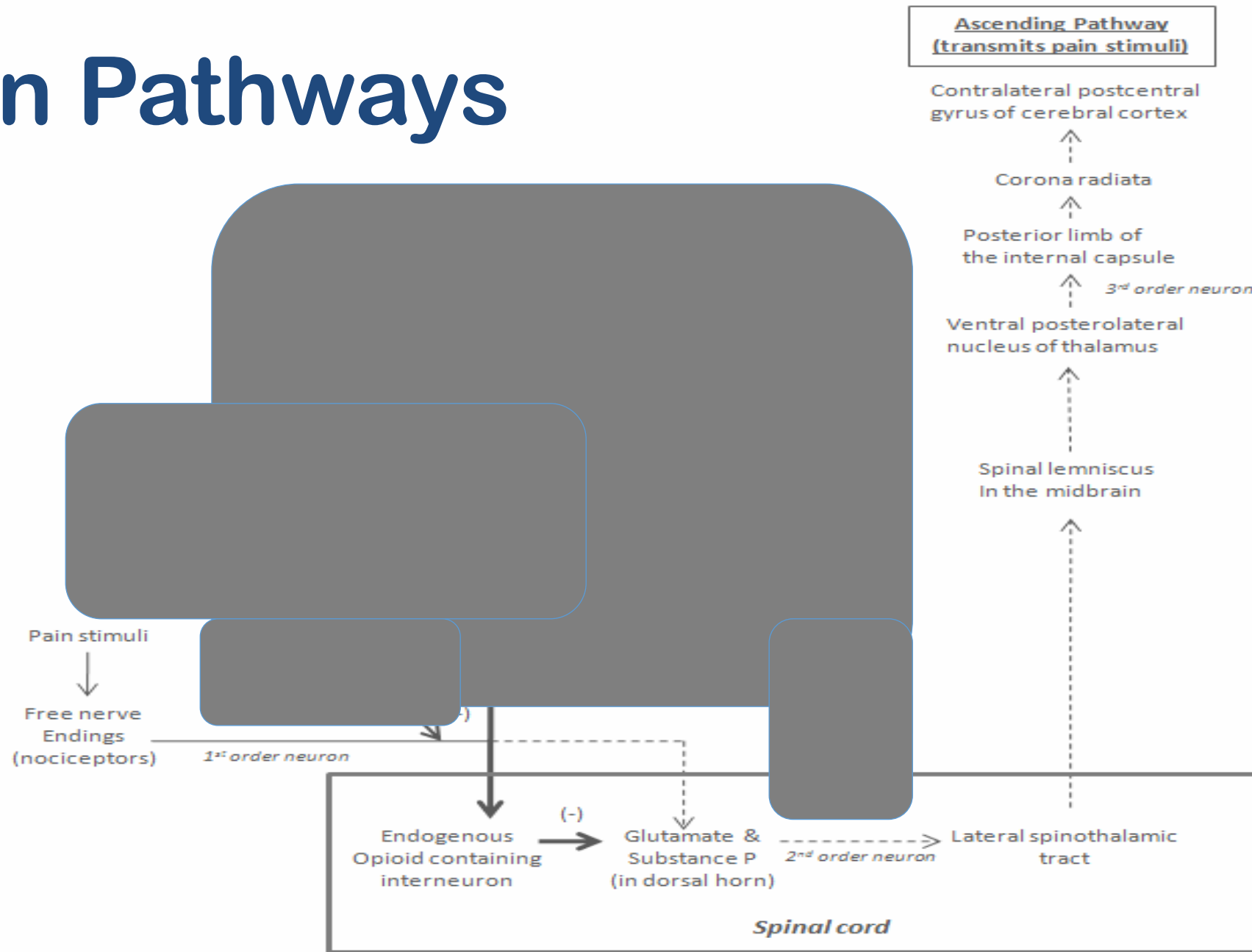


Figure 1. Mechanism of opioid induced analgesia.
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Opioid Analgesia

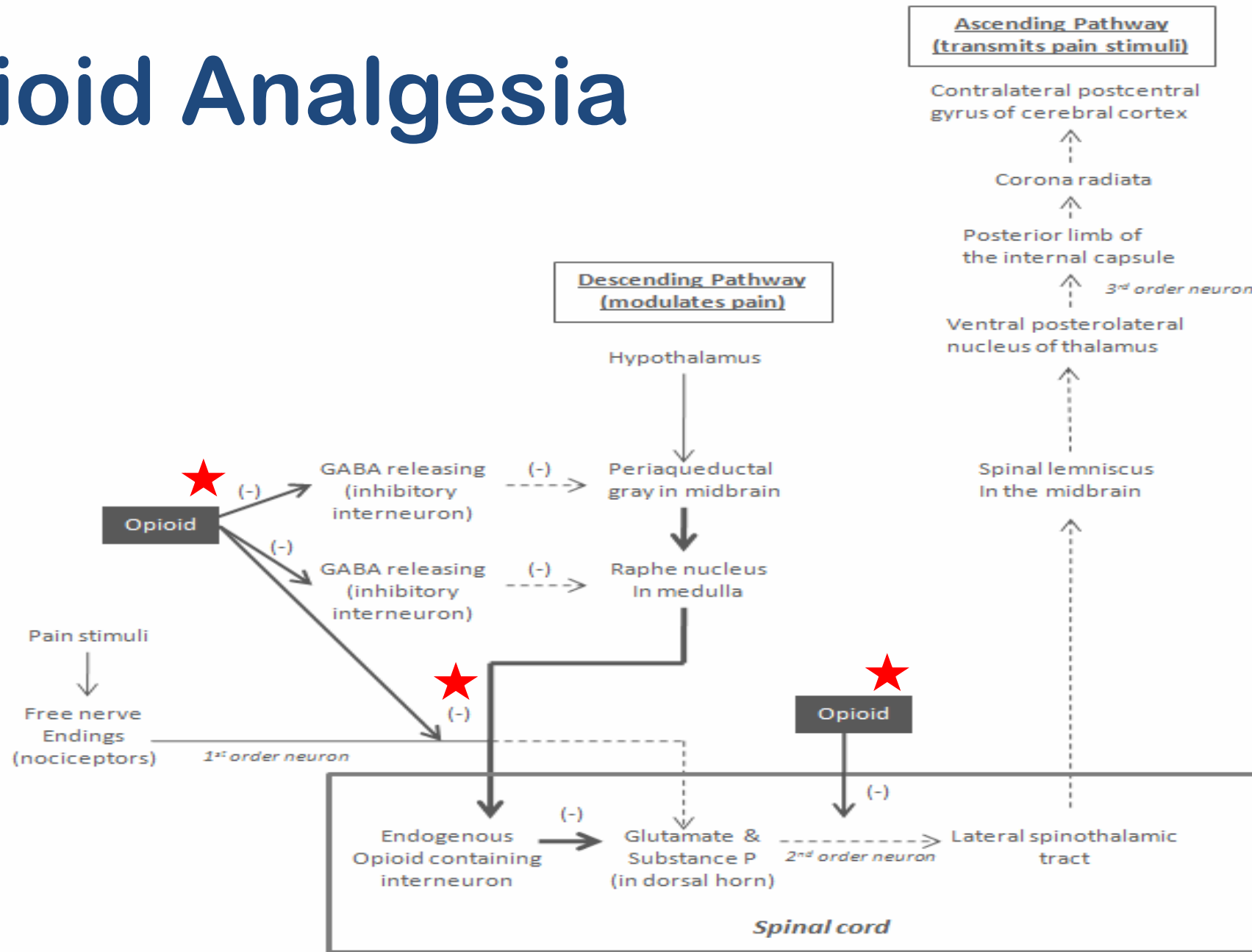


Figure 1. Mechanism of opioid induced analgesia.
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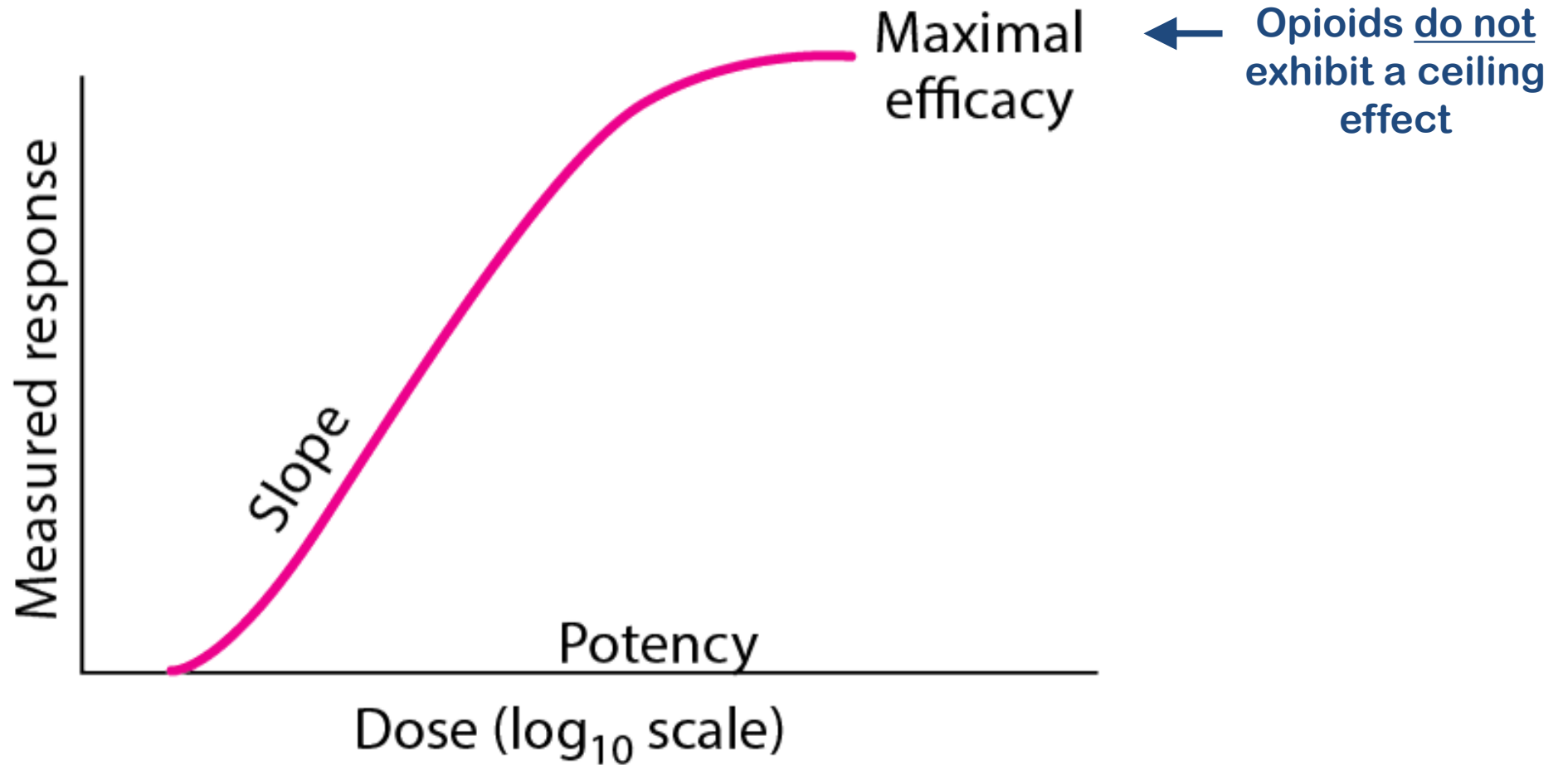


Ceiling effect

- Independent variable (dose) no longer has effect on dependent variable (analgesia)
- Plateau on dose response curve
- Acute organ toxicities



The Dose Response Curve

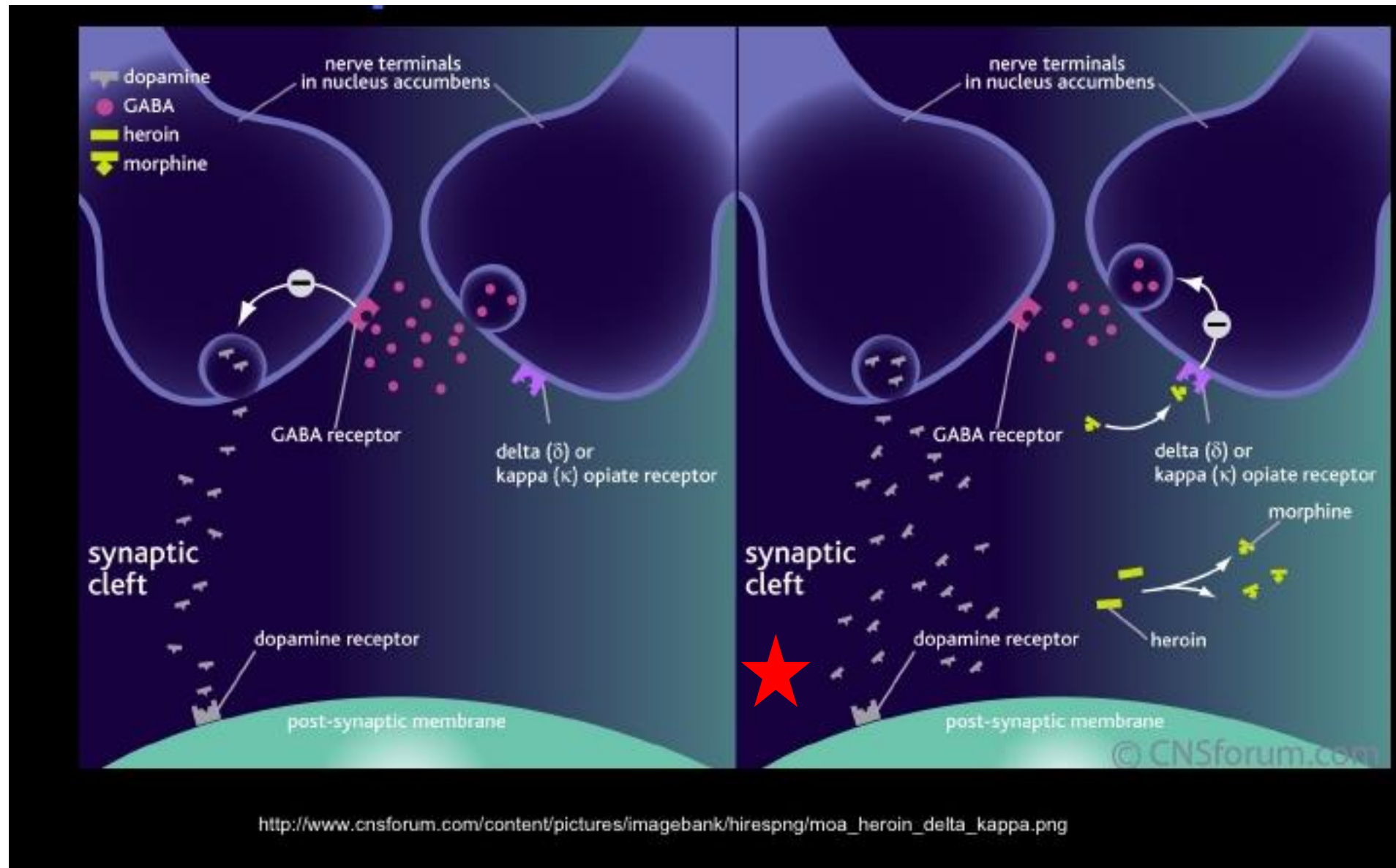


DRUGS OF ABUSE

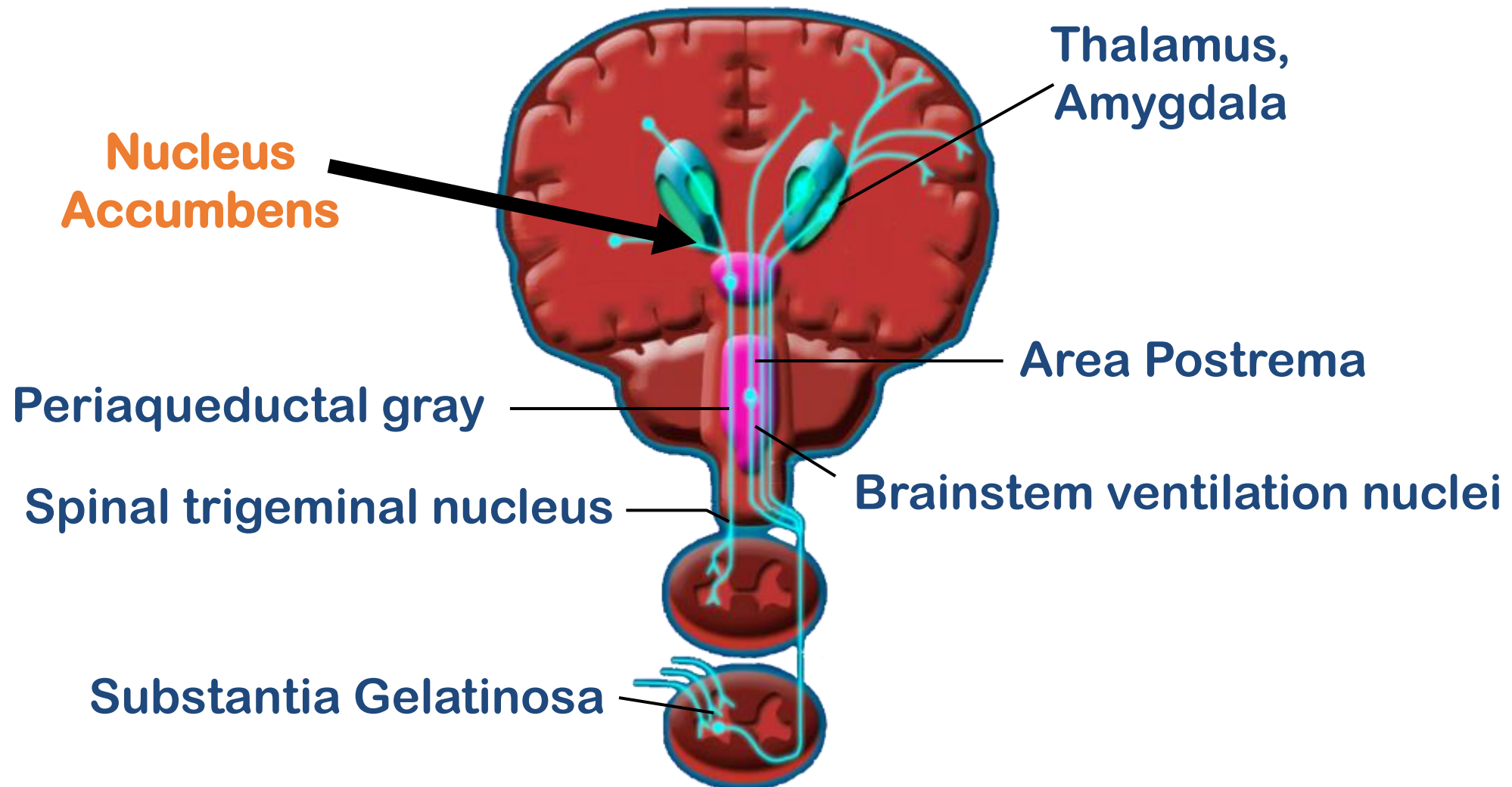
What neurotransmitter links them?

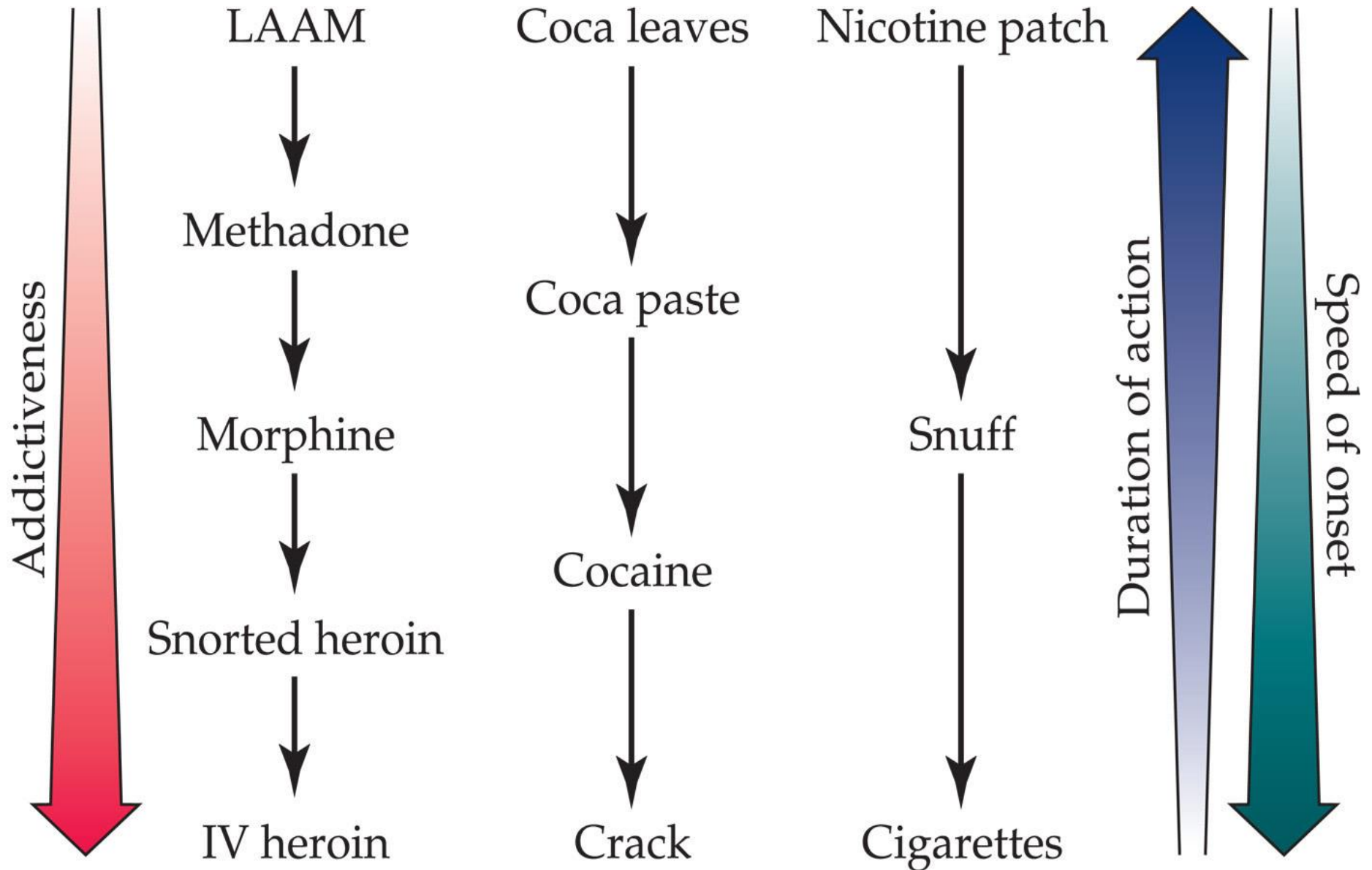


IN A WORD...DOPAMINE



Opioid Receptor Areas of High Density





PSYCHOPHARMACOLOGY 2e, Figure 9.6
© 2013 Sinauer Associates, Inc.



TOLERANCE VS. ADDICTION

Diction is important



What is Addiction?

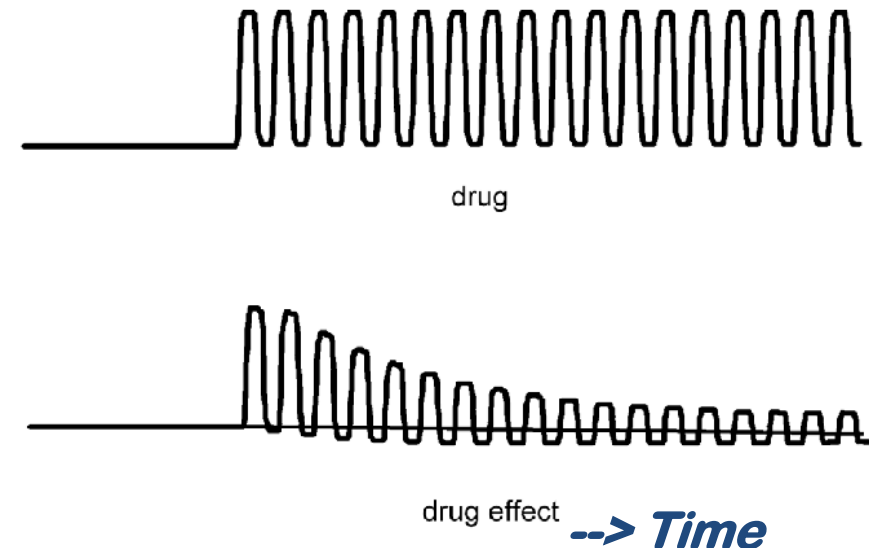
- **Chronic, relapsing disorder**

“A behavioral pattern pattern of drug use, characterized by overwhelming involvement with the use of a drug (compulsive use), the securing of its supply, and a high tendency to relapse after withdrawal”

- Goldstein, 1989

What is Tolerance?

- **Loss of drug effect with chronic dosing**



**Substance
Dependence**

≠

**Substance
Use Disorder**

- Patient with diabetes → Insulin
- Patient in pain → Analgesic
- Goal is to improve:
 - Well being
 - Function
 - Quality of life



The Diagnostic and Statistical Manual of Mental Disorders

5th Edition

(DSM-5)

11 items:

- Taking larger amounts or taking drugs over a longer period than intended.
- Persistent desire or unsuccessful efforts to cut down or control opioid use.
- Spending a great deal of time obtaining or using the opioid or recovering from its effects.
- Craving, or a strong desire or urge to use opioids
- Problems fulfilling obligations at work, school or home.
- Continued opioid use despite having recurring social or interpersonal problems.
- Giving up or reducing activities because of opioid use.
- Using opioids in physically hazardous situations.
- Continued opioid use despite ongoing physical or psychological problem likely to have been caused or worsened by opioids.
- Tolerance (i.e., need for increased amounts or diminished effect with continued use of the same amount)
- Experiencing withdrawal (opioid withdrawal syndrome) or taking opioids (or a closely related substance) to relieve or avoid withdrawal symptoms.

DSM-5 Criteria for Diagnosis

1. Taking more than intended
2. Trying to cut down

3. Spending time
4. Craving
5. Recurrent use

6. Continued use even w/ problems
7. Important activities impacted
8. Use in hazardous situations
9. Use despite understanding bad

10. Tolerance
11. Withdrawal

Loss of Control

Preoccupation with Drugs

Use Despite
Consequences

Tolerance and Withdrawal

Scoring:
2-3 = mild
4-5 = moderate
> 6 = severe

Maladaptive pattern of use >12 months along with significant impairment/distress



Opioid Curriculum: Year 1, Section 1, Part 3b

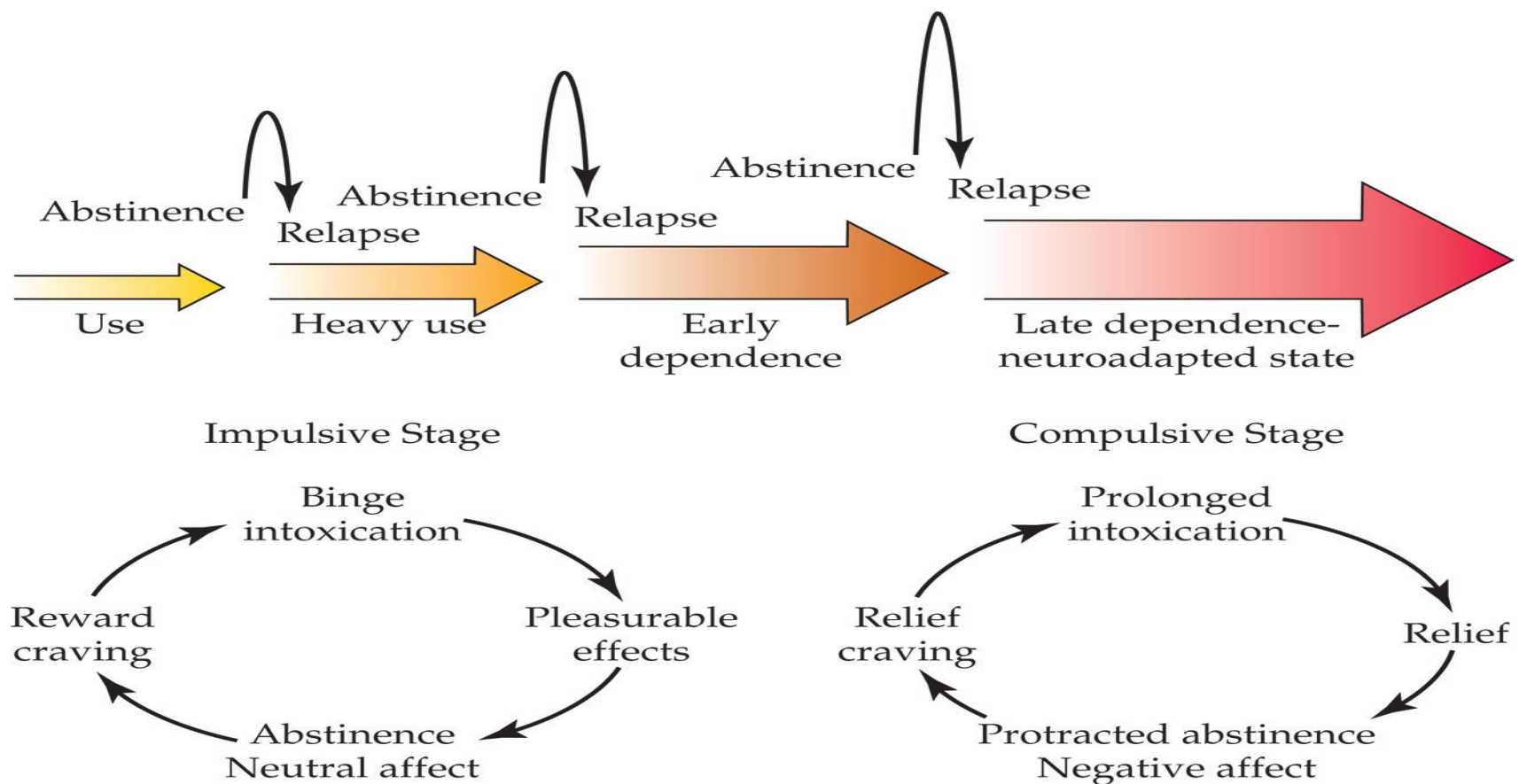
UNDERSTANDING SUD

Jessica Childs, PhD

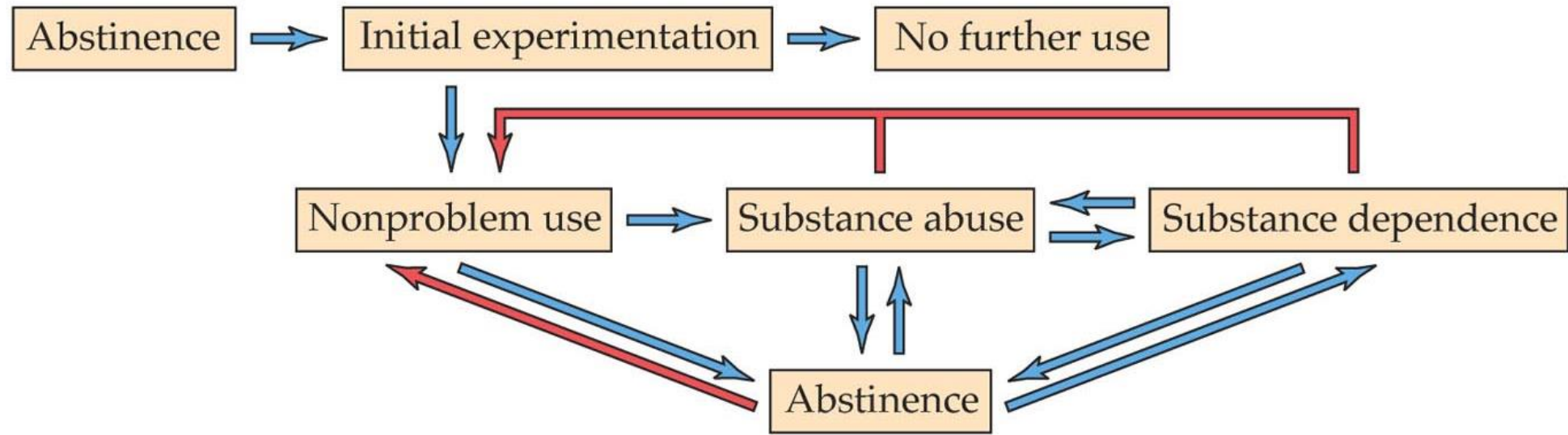
Postdoctoral Fellow, Neurobiology Department



Developing Substance Use Disorder

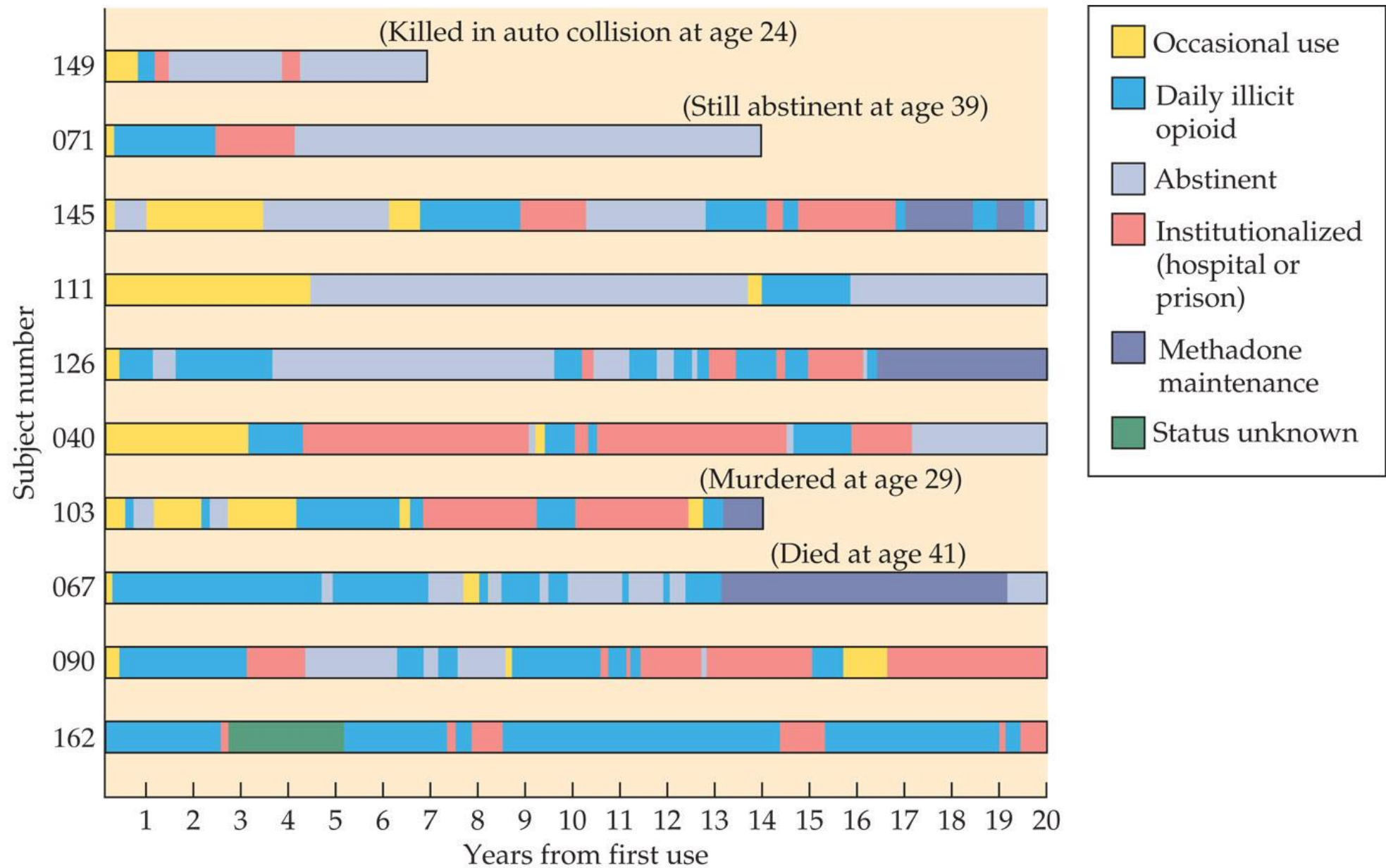


Continuum of Drug Use



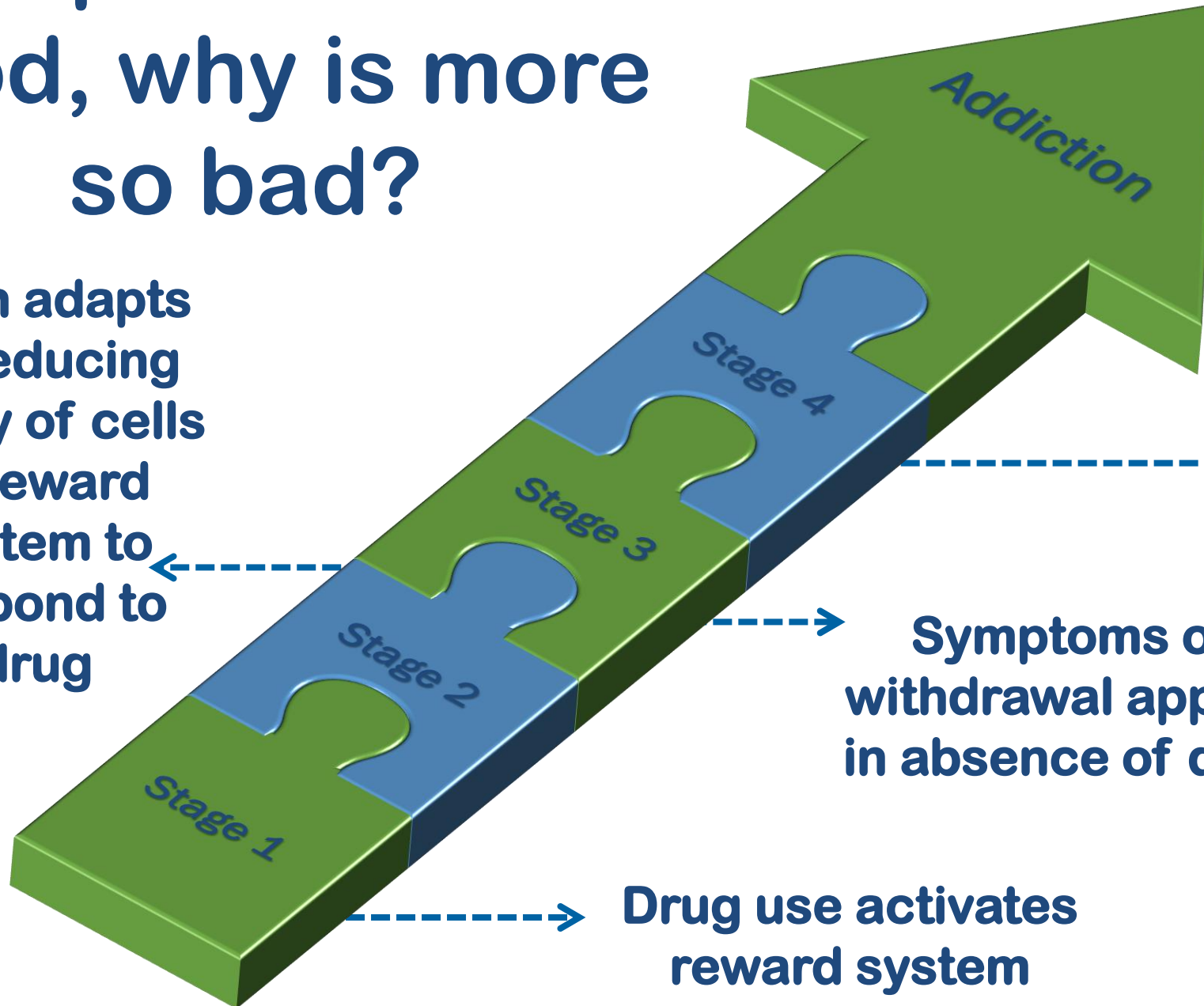
SUBSTANCE ABUSE = SUD





If dopamine is so good, why is more so bad?

Brain adapts by reducing ability of cells in reward system to respond to drug

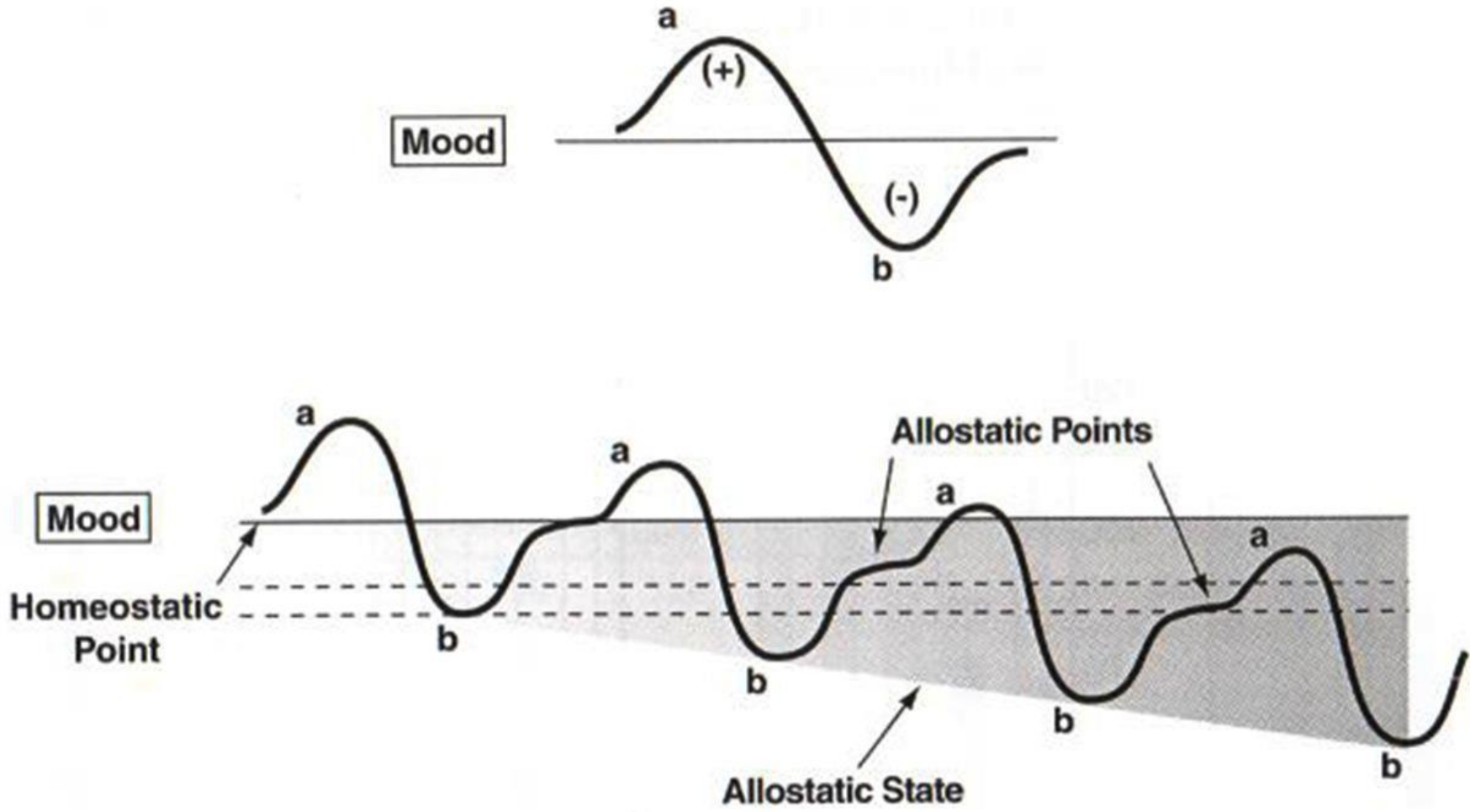


Drug use activates reward system

Symptoms of withdrawal appear in absence of drug

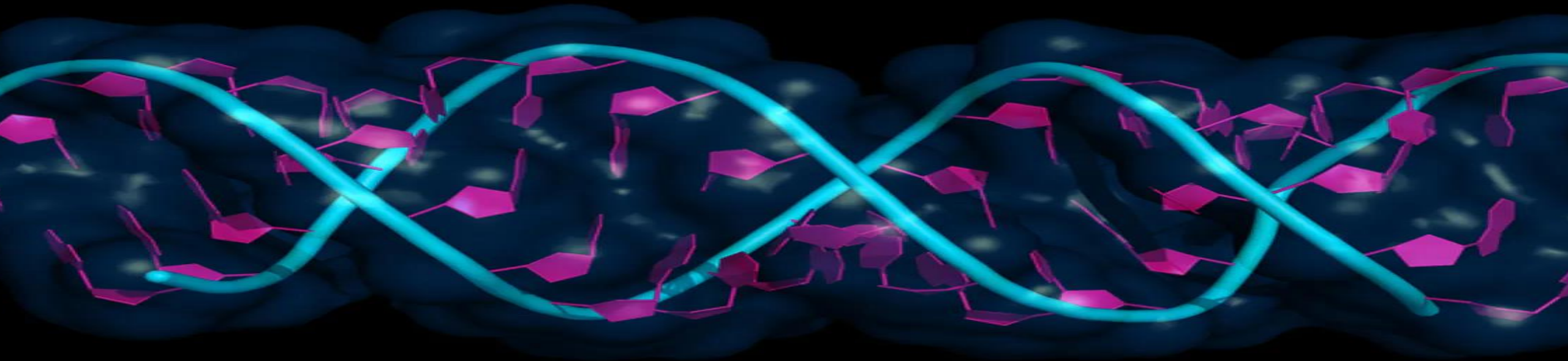
Chronic disease: compulsive drug seeking despite harmful consequences

Opponent Process Model



How do drugs of abuse lead to persistent changes in neuronal function?

- Lead to incredibly long-lasting changes in cell function, neuronal circuits, and ultimately behavior



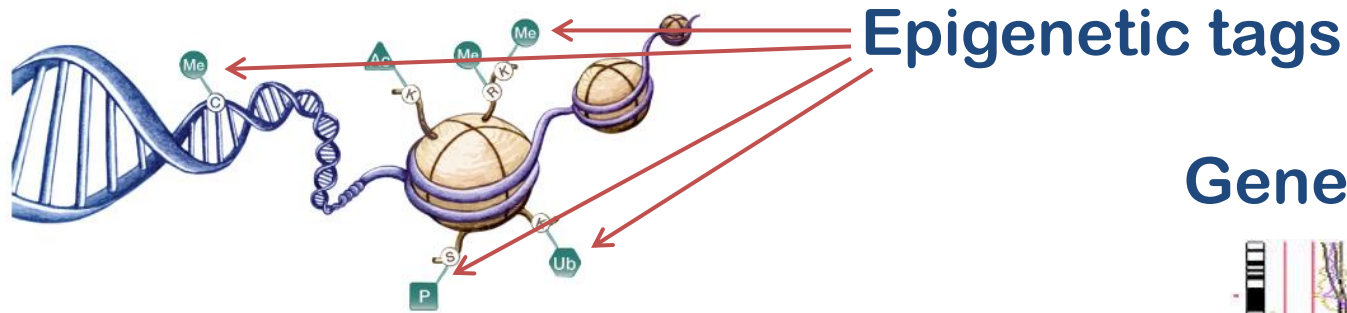
- Cell function changes via epigenetics

Definition of epigenetics

- Modulation of chromatin → Change gene expression
- Epigenetics is “beyond on your genes”
- Heritable



Epigenetics in action:

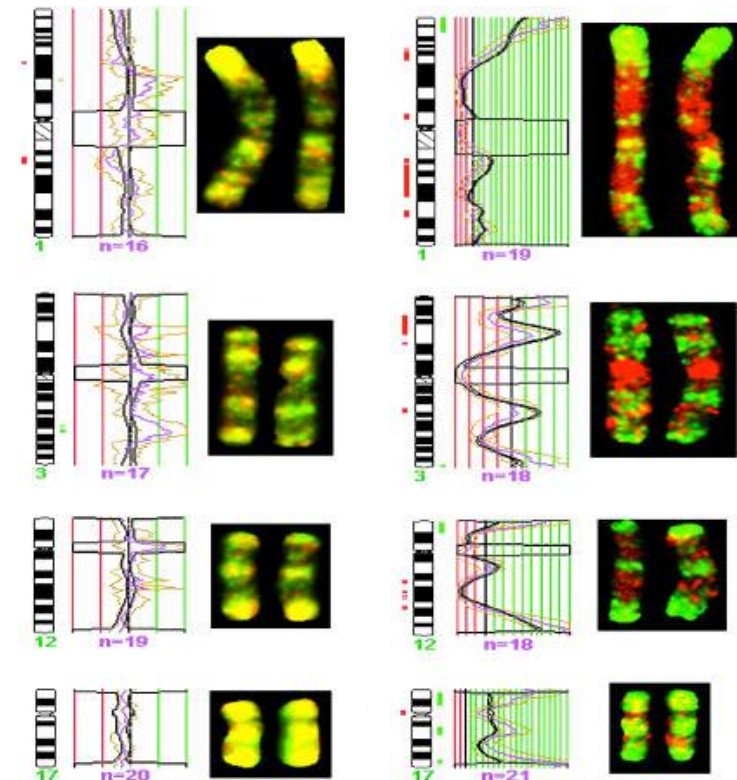


Epigenome:

Collection of epigenetic tags

Tags change with experiences, environmental interaction, and even our diet!

Genetically identical twins



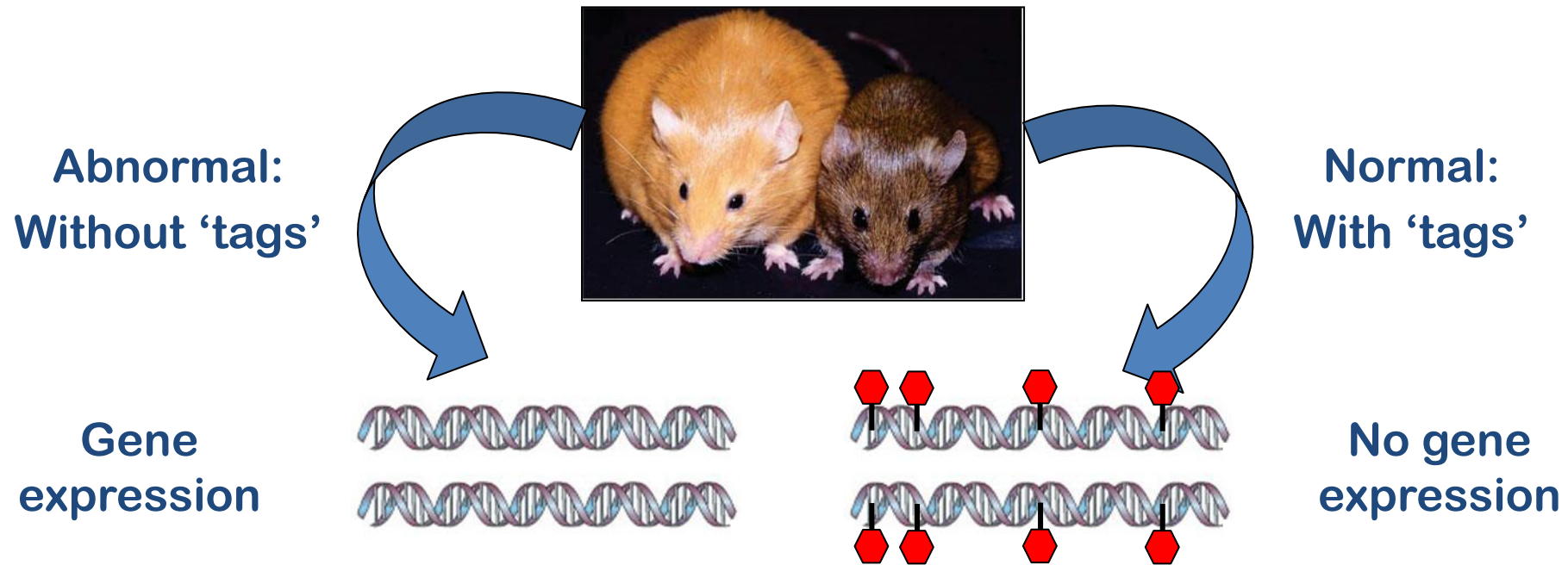
3 year old twins

50 year old twins



Epigenetics in action:

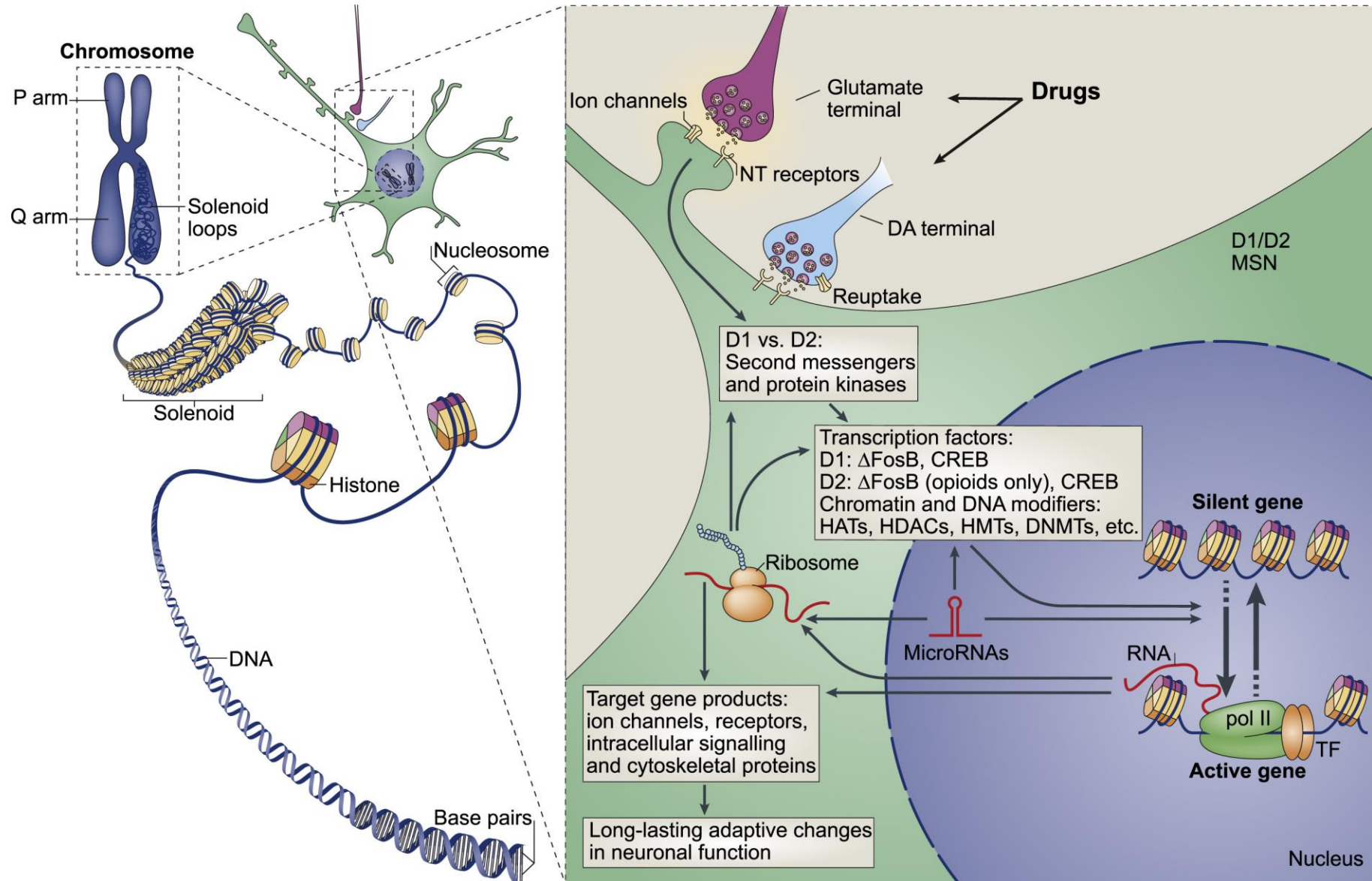
Epigenetics encodes information from your diet



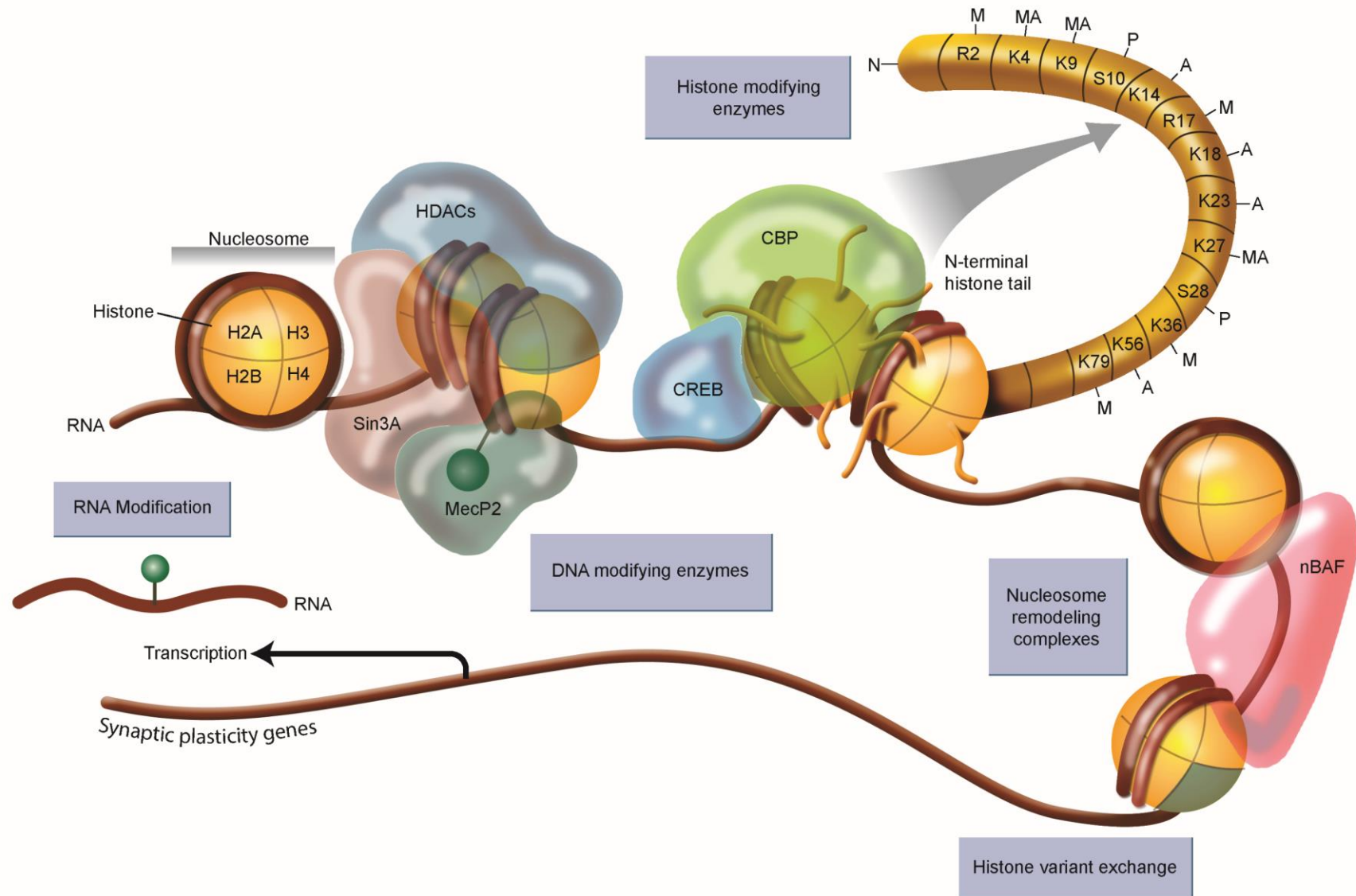
- 1) Feed pregnant yellow mice folic acid = most pups born normal
- 2) Feed pregnant yellow mice Bisphenol A (BPA) = most pups born abnormal



Drugs of abuse and epigenetics



Drugs of abuse and epigenetics

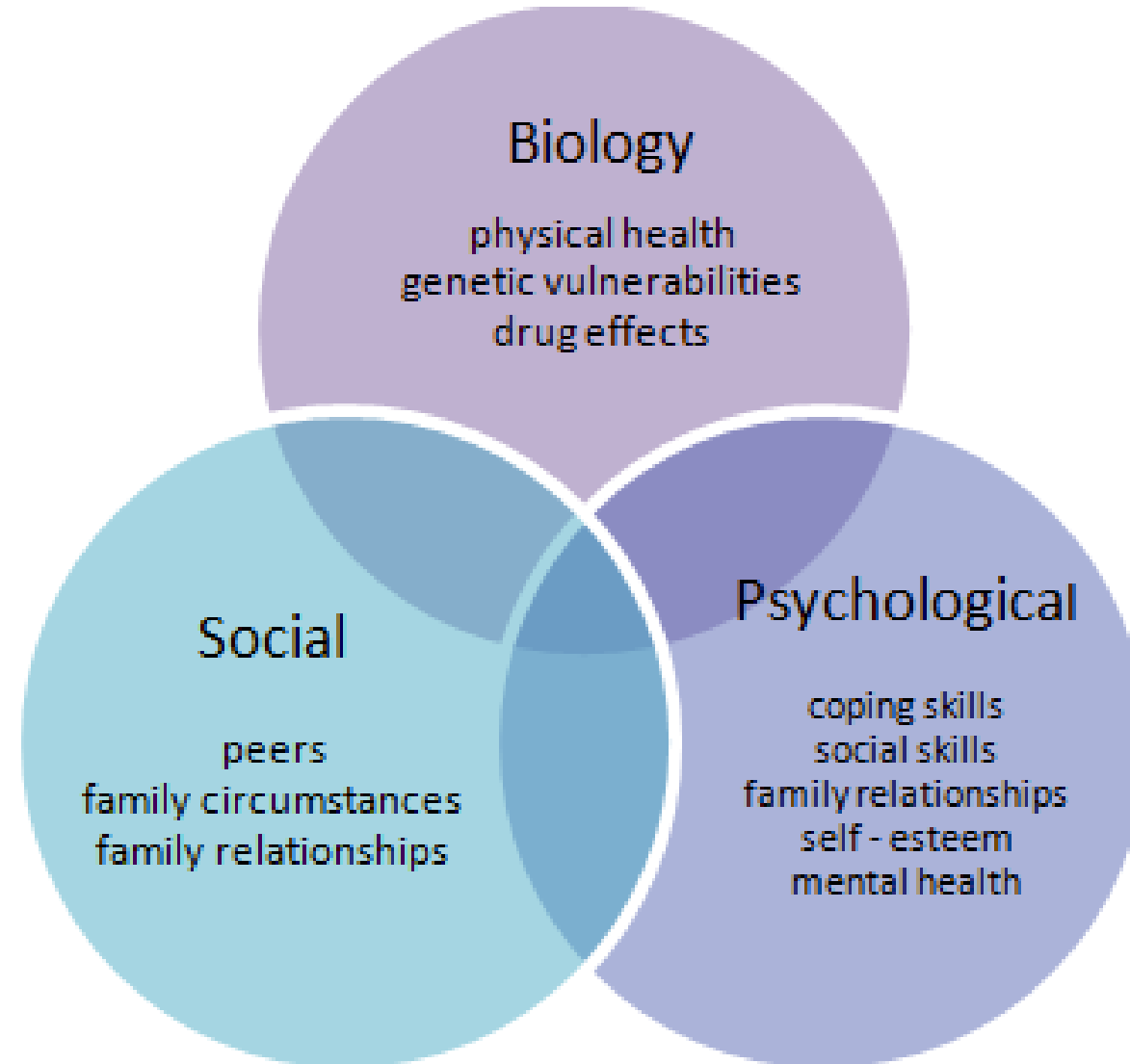


Drugs of abuse and epigenetics

- Opioids and all drugs of abuse lead to changes in epigenetic machinery
- Front-line treatments like methadone or buprenorphine also affect epigenetics
- But when and how do epigenetic alterations lead to persistent changes in cell?



The Biopsychosocial Model



Biopsychosocial Approach to Substance Use/Abuse

Neurobiological Model

- Addiction as a “brain disease”
 - Neurotransmitter imbalance (dopamine)
 - Activation of specific brain areas

Psycho-Social Systems

- Influence of psychological, social, cultural and interpersonal factors
 - Positive reinforcing effects
 - Discriminative subjective effects
 - Stimuli conditioned to drug effects
 - Aversive effects of drugs



Biopsychosocial Approach to Substance Abuse

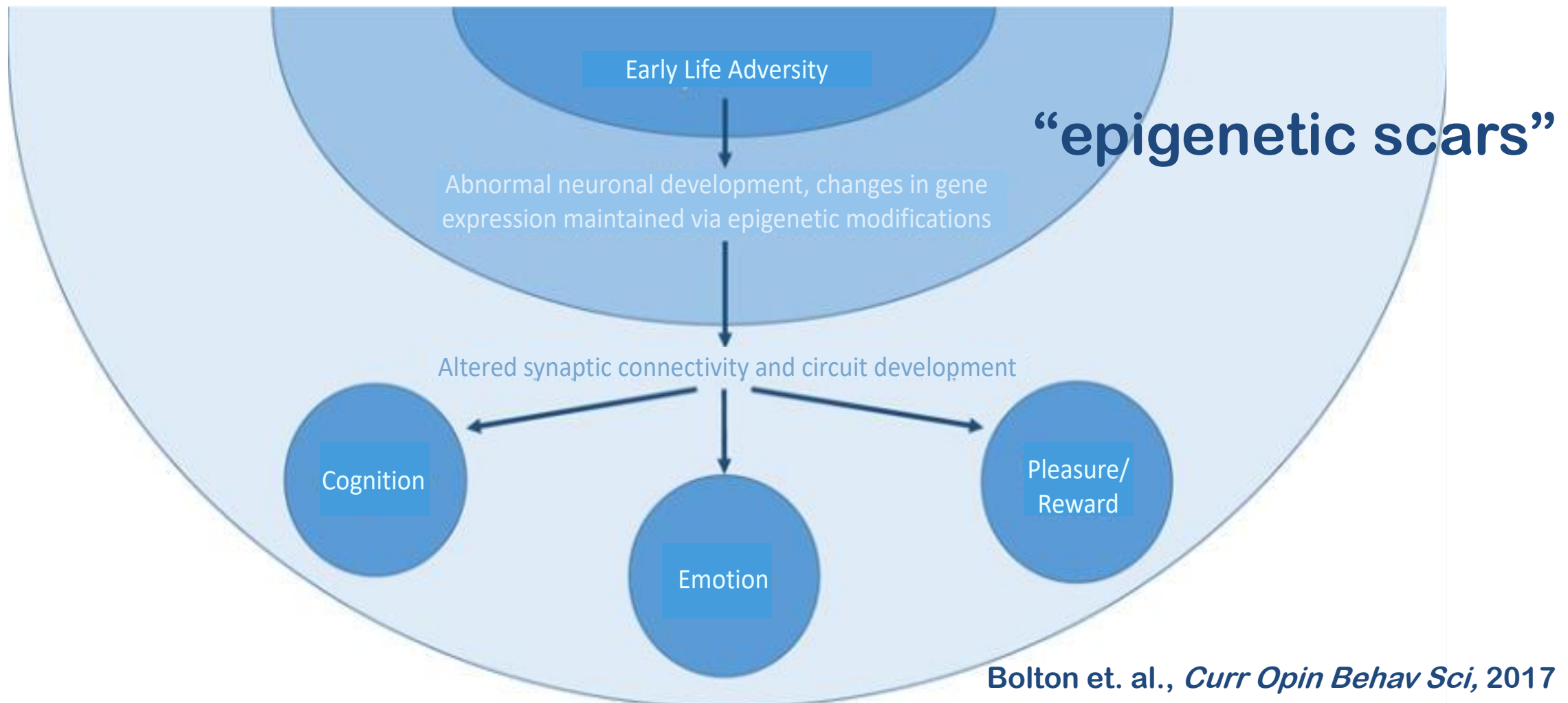


A dynamic interplay between many factors:

- Neurobiological
- Psychological
- Social

Adverse Early Life Experiences

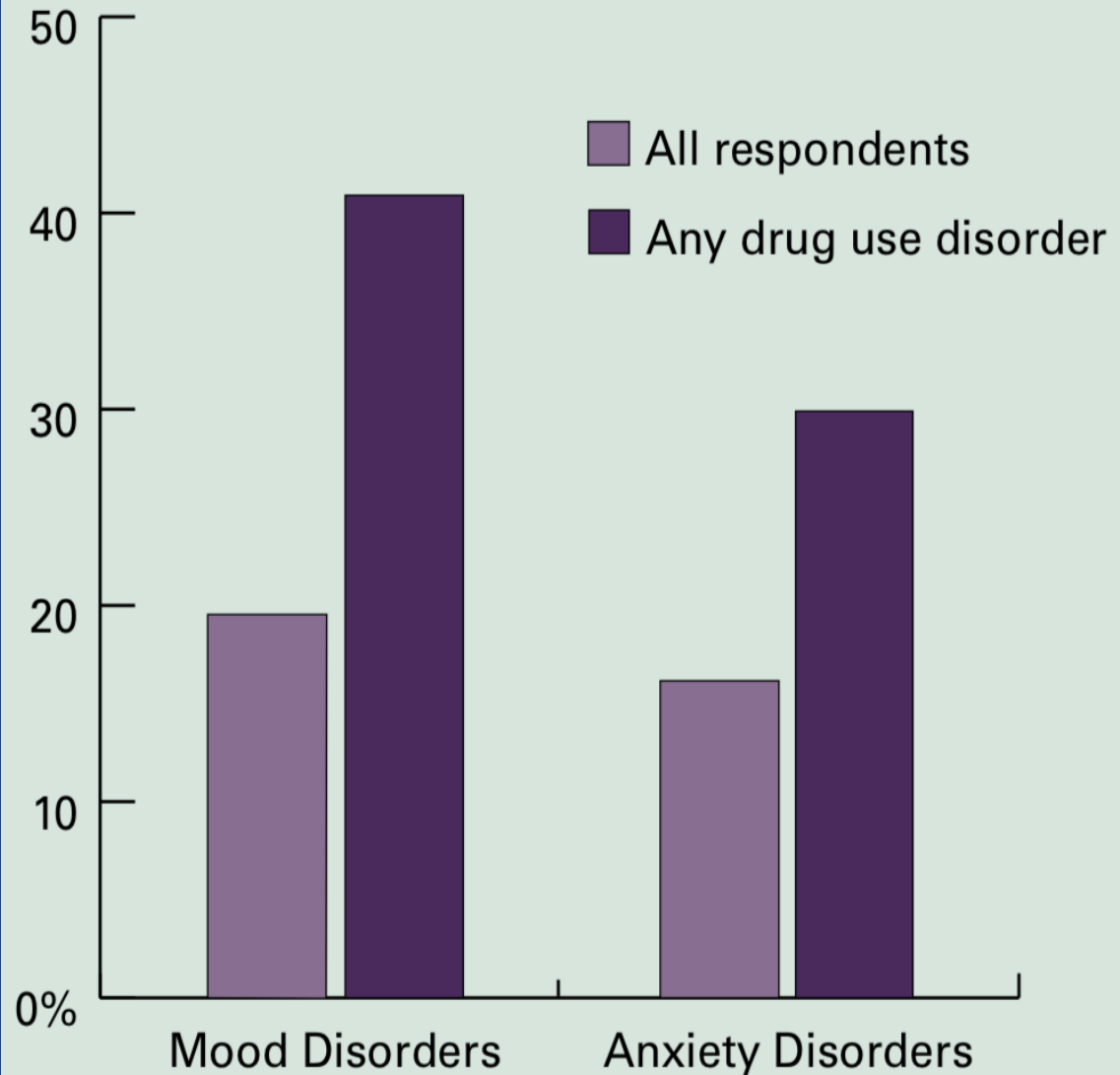
↑ Vulnerability to Opioids



Risk Factors: Personality Traits that May Predispose Addiction

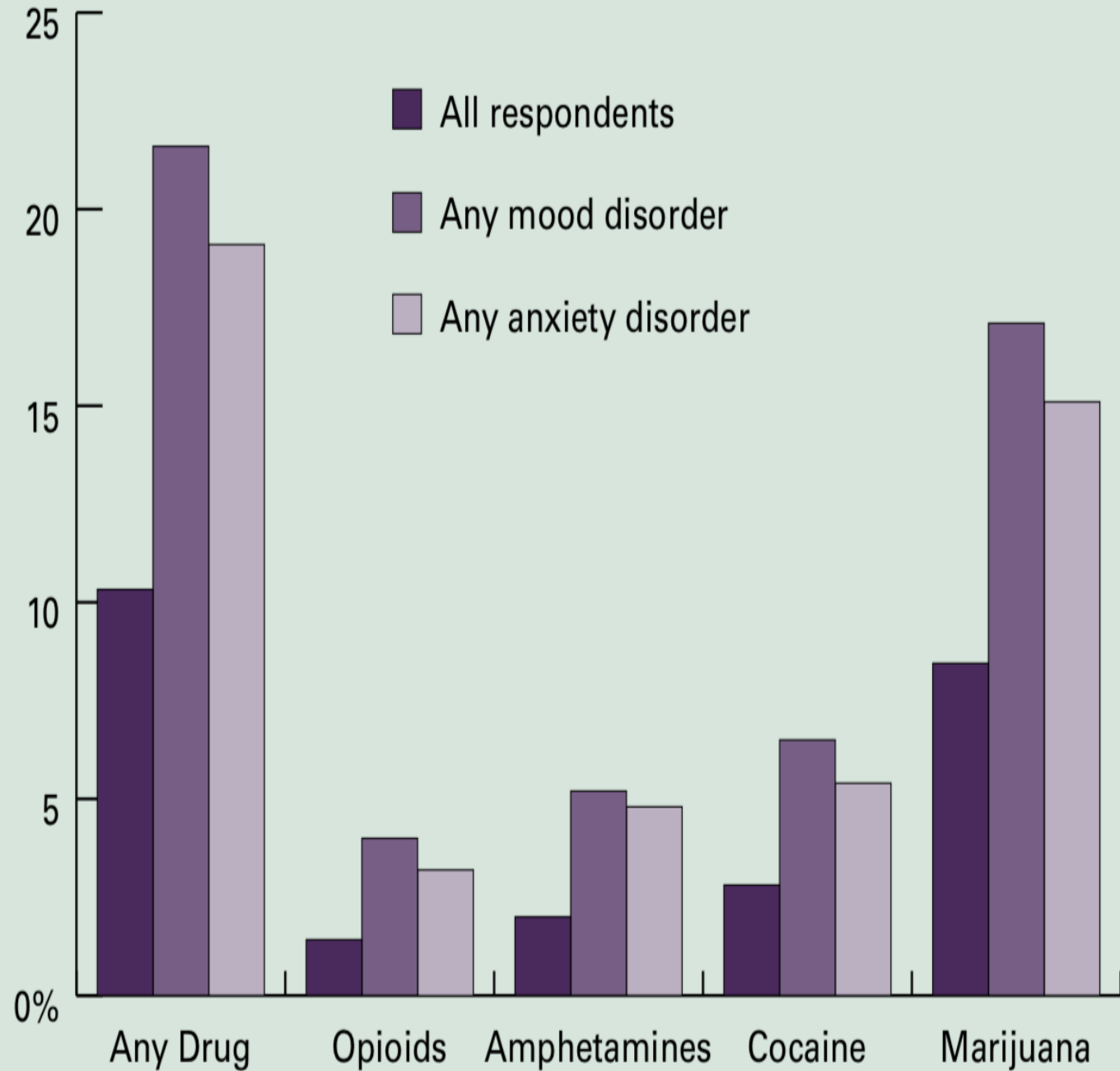
- Stress reactivity, anxiety
- Behavioral disinhibition
 - Impulsivity
 - Anti-sociality
 - Aggressiveness
 - Low levels of harm avoidance
- Reward sensitivity
- Genetic allelic variation

Higher Prevalence of Mental Disorders Among Patients With Drug Use Disorders



High Prevalence of Dependence with Mood + Anxiety Disorders

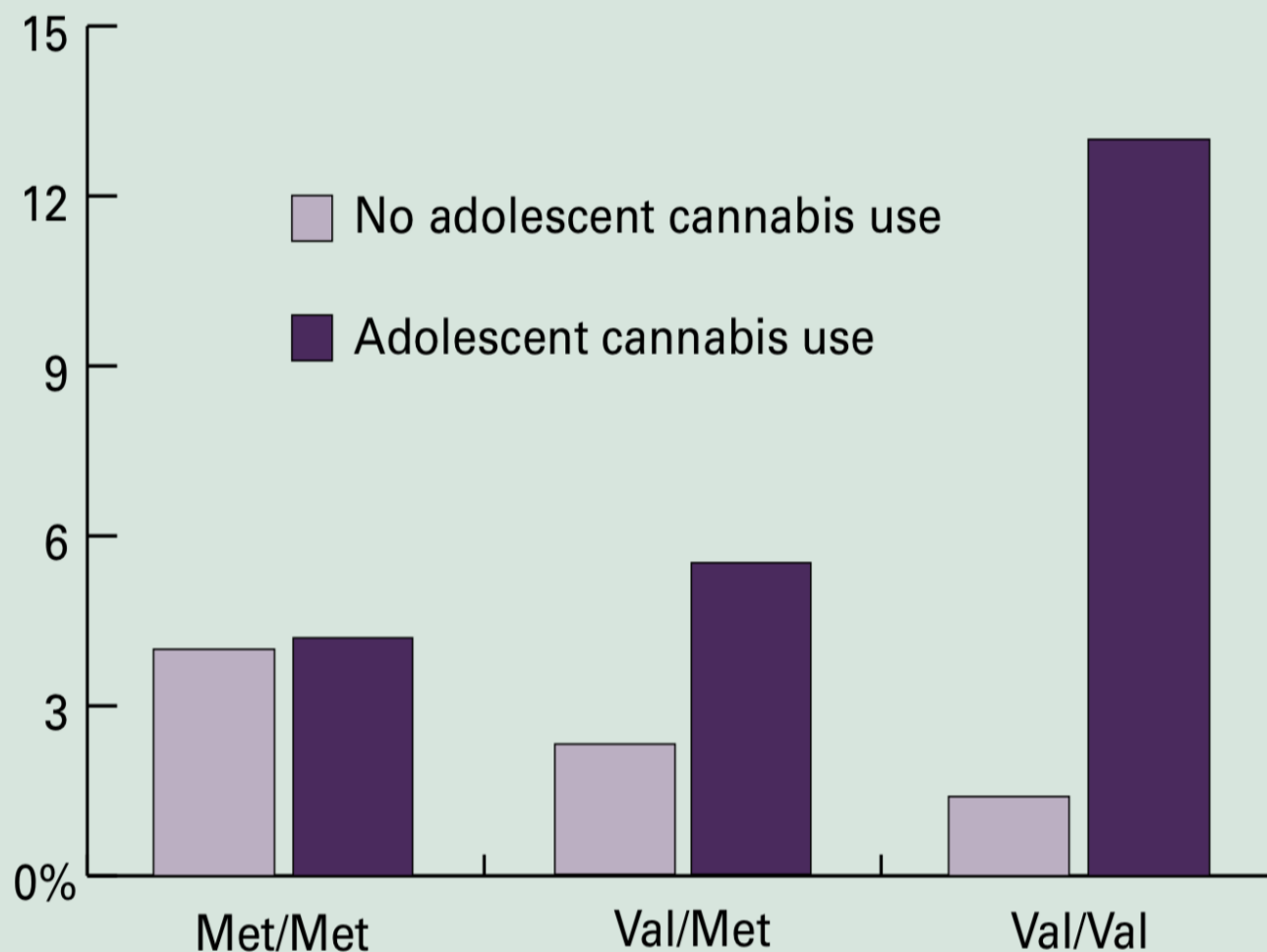
Comorbidity dependence with Psychiatric Disorders



Comorbidity of Dependence with Psychiatric Disorders

Gene + Environment Interaction

Percentage of Individuals Meeting Diagnostic Criteria for Schizophreniform Disorder at Age 26



Source: Caspi A, Moffitt TE, Cannon M, et al., 2005.

Protective Factors

Reduce the likelihood that an individual will develop SUD
OR
Improve likelihood of stable abstinence

- **Absence of risk factors**

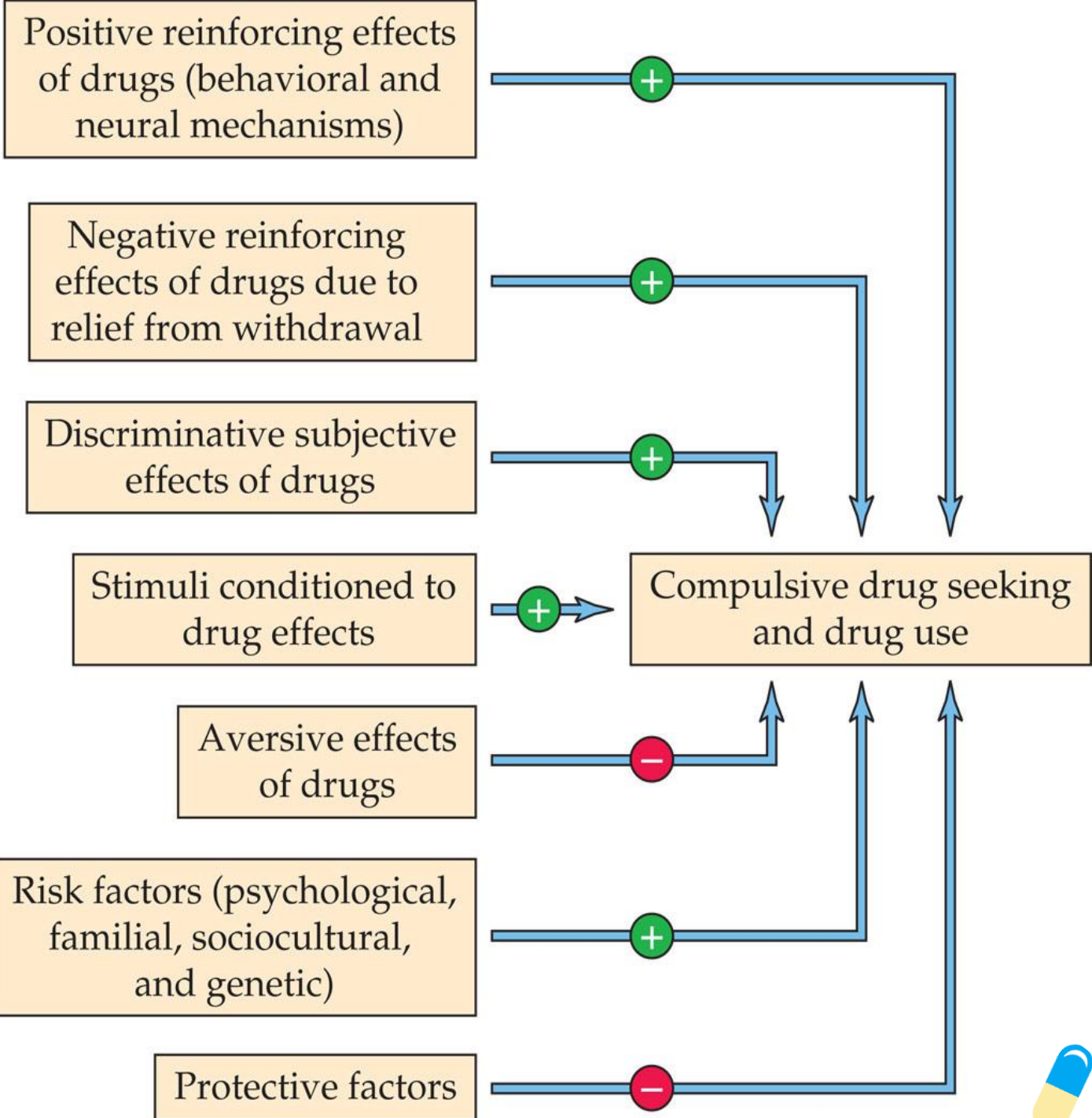


Family + Social Support
Safe living environment
No genetic predisposition
Financial stability

- **Personal Factors**



Factors that can Promote or Protect from Drug Use and Abuse



COVID-19 and Drug Abuse

U.S. Drug-Overdose Deaths Soared Nearly 30% in 2020, Driven by Synthetic Opioids

Fentanyl, along with isolation and stress from Covid-19 pandemic, propelled surge, experts say

- 54% increase in opioid overdoses since 2019
- Sharpest increase in drug overdoses in 30 years
 - Synthetic Opioids
 - Methamphetamine
 - Cocaine

Biopsychosocial Perspective



50x more potent



Access to treatment + support networks

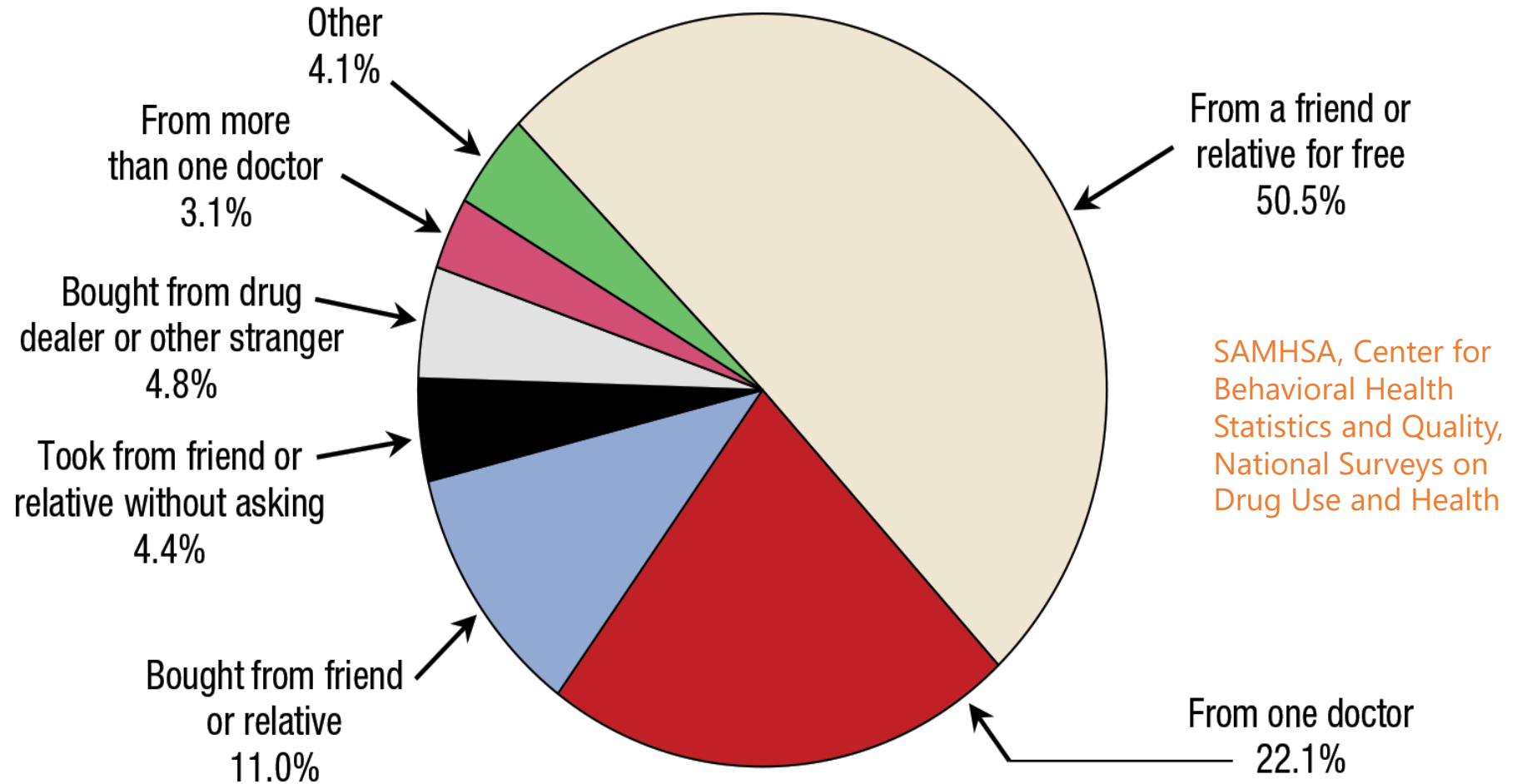
Mental health

OPIOID USE DISORDER

How do patients become exposed to opioids?

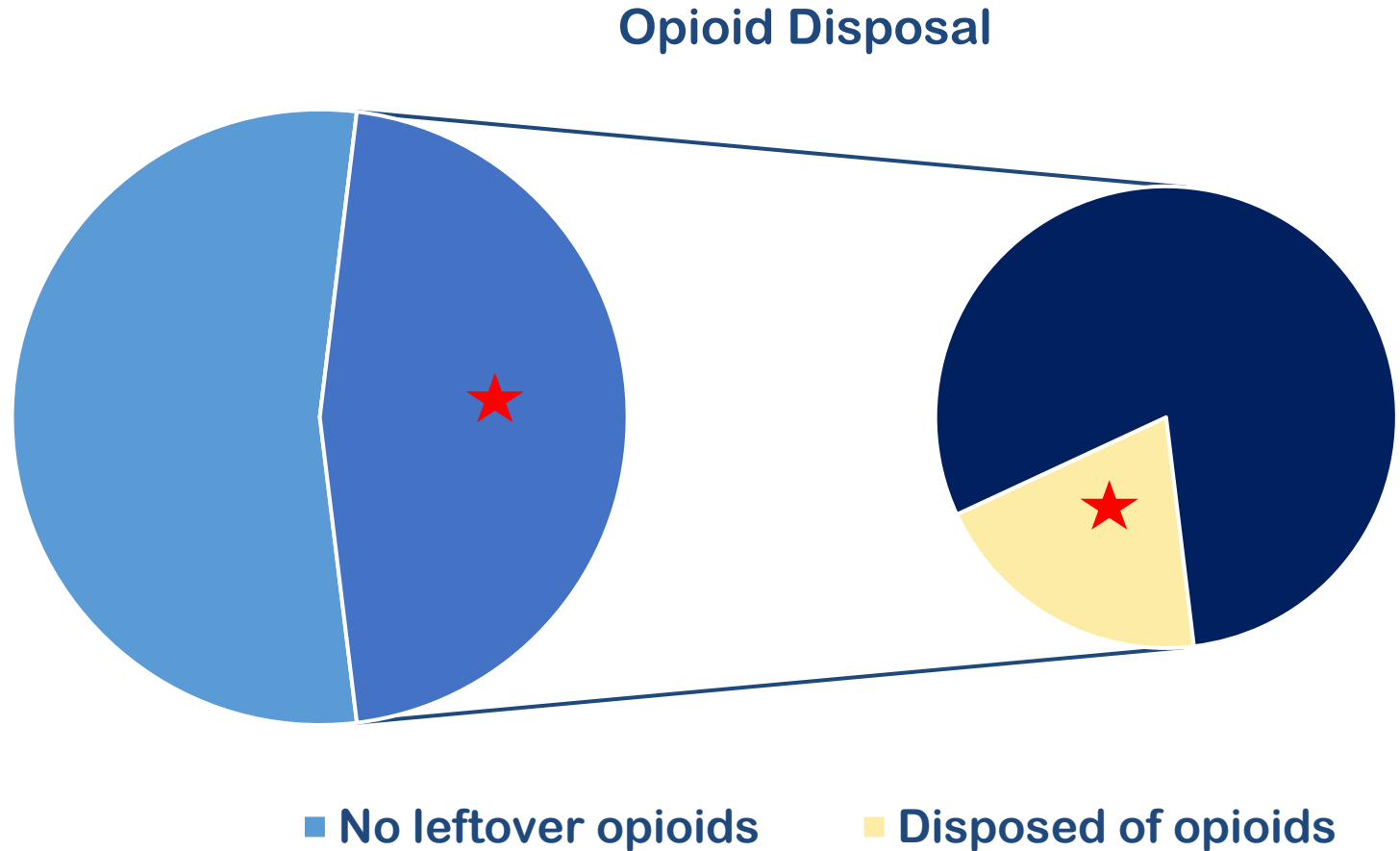


Recreational Opioid Source



Leftover Opioids

- Nationally represented survey
- 49% of patients 50-80 years old had residual opioid
- Only 20% turned those in for disposal



Schedule I	Most potential for abuse and dependence
Schedule II	High potential for abuse and dependence
Schedule III	Moderate potential for abuse and dependence
Schedule IV	Low potential for abuse and dependence
Schedule V	Lowest potential for abuse and dependence

DEA scheduling system

- Do not confuse schedule with analgesic potential
- Potency of opioids related but not equal



Schedule I	Most potential for abuse and dependence No medicinal qualities Heroin, LSD, Marijuana Ecstasy, Peyote
Schedule II	High potential for abuse and dependence Some medicinal qualities Vicodin, Cocaine, Meth, OxyContin, Adderall
Schedule III	Moderate potential for abuse/dependence Acceptable medicinal qualities Doctor's prescription required Tylenol with Codeine, Ketamine, Steroids, Testosterone
Schedule IV	Low potential for abuse and dependence Acceptable medicinal qualities Prescription required - fewer refill regulations Xanax, Darvon, Valium, Ativan, Ambien, Tramadol
Schedule V	Lowest potential for abuse/dependence Acceptable medicinal qualities Prescription required - fewest refill regulations Robitussin AC, Lomotil, Motofen, Lyrica

Schedule II

- No refills
- Tamper resistant paper
- 2 factor authentication

Schedule III

- 2 refills
- Must check PDMP

Schedule IV

- 2 refills

Schedule V

- 5 refills



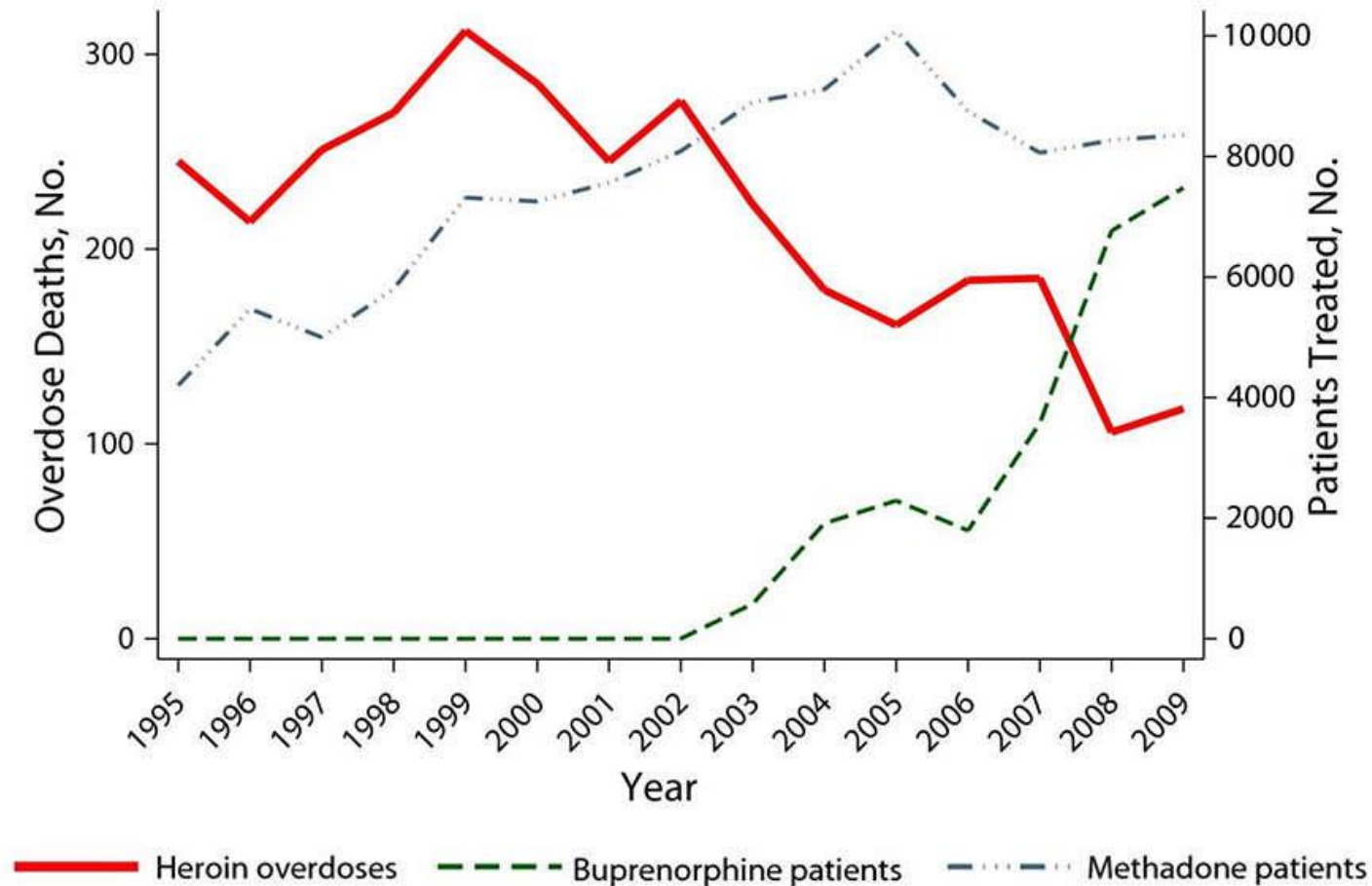
TREATMENT FOR SUD

What now?



Medication Assisted Treatment (MAT) Decreases Opioid Use

MAT REDUCES HEROIN OD DEATHS



Methadone

- Achieves steady-state due to long half life
- Prevents withdrawal symptoms
- Reduces cravings
- No euphoria once patient achieves tolerance



Buprenorphine

- Blocks effects of other opioids
- Reduces withdrawal symptoms and cravings
- Buprenorphine treatment
 - Detoxification or maintenance
 - Provider previously needed x-waiver from DEA
- Higher retention in those with ≥ 1 psychiatric condition



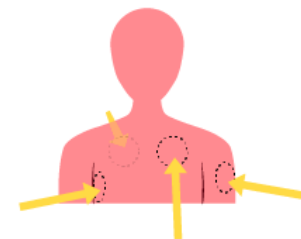
ORAL



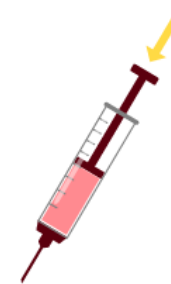
SUBLINGUAL



BUCCAL



TRANSDERMAL



INJECTION



INTRANASAL



Naltrexone

- Blocks effects of opioids and prevents euphoria
- Outpatient treatment



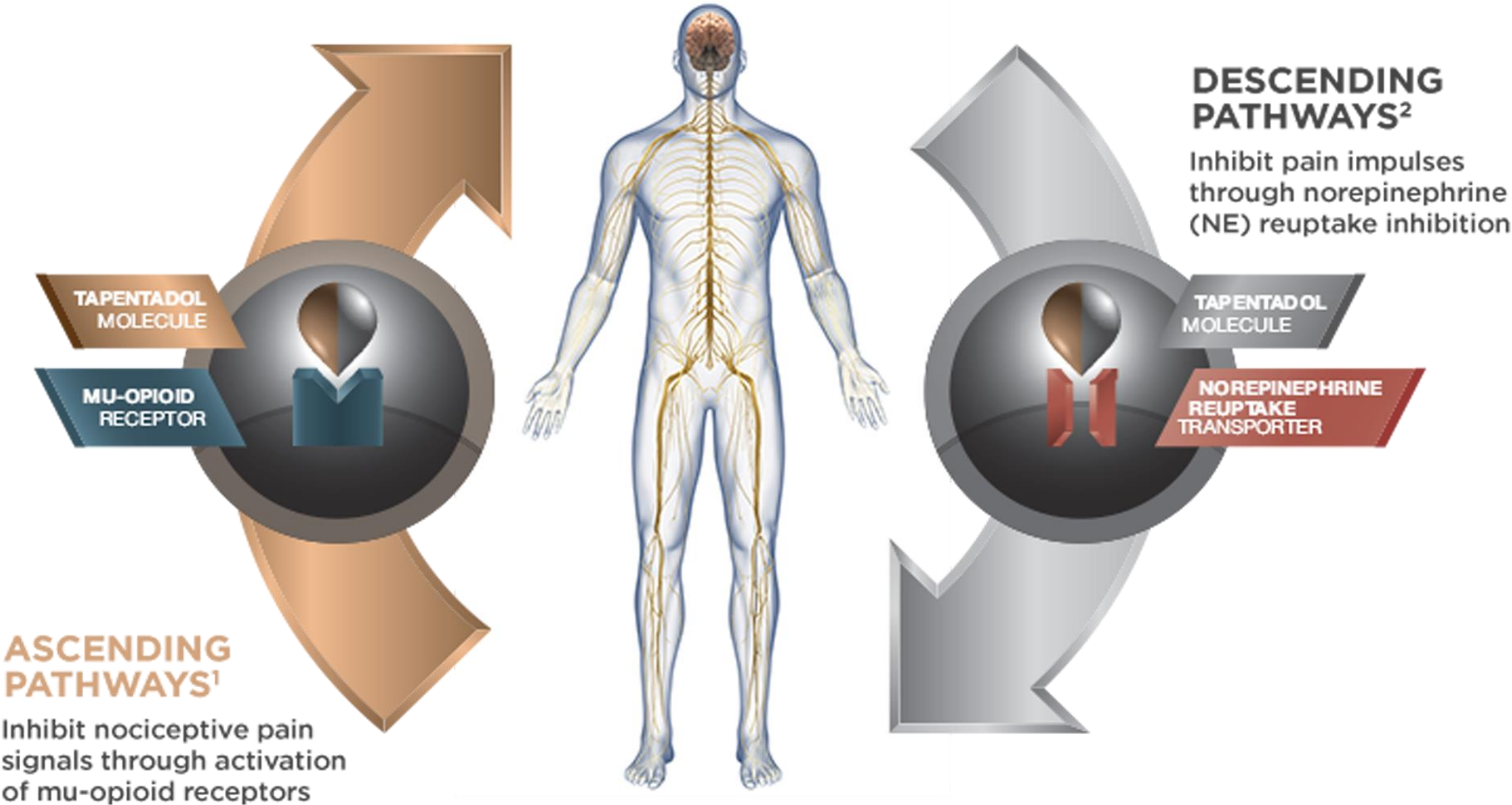
Daily 50 mg PO



Monthly 380 mg IM



Opioids with less addictive potential



Evidence Based Care for Opioid Use Disorder

An interpersonal and multifaceted plan is **KEY**



Personalized diagnosis and treatment planning tailored to the individual and family



Long-term management – Addiction is a chronic condition with the potential for both recovery and recurrence



Access to FDA-approved medications



Effective behavioral interventions delivered by trained professionals



Coordinated care for addiction and other conditions



Recovery support services, such as mutual aid groups, peer support specialists, and community services



Further Reading

NIH – HEAL Initiative

National Institute on Drug Addiction

TOPCARE

UC Irvine Center for Addiction Neuroscience (ICAN)

Impact of Cannabis Across the Lifespan (ICAL)

