

# Comorbid Psychiatric Disorders among Patients with Substance Use Disorder

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# Introduction

- Definition
  - Concurrent (Axis I) non-substance use disorders
- Observations:
  - Highly prevalent
  - Worse clinical and functional outcome
  - Do not receive adequate treatment
  - Tend to use more costly services

# Epidemiology

- Several decades of research
  - Both in treatment seeking populations and community
- Co-occurring psychiatric disorders far more than expected

# Epidemiology

- Risk factors include:
  - Female sex
  - Older age
  - Poverty and low socio-economic status
  - History of incarceration
  - Urban residence

# Epidemiology

- Among people with a psychiatric disorder, 30% had a co-occurring Substance Use Disorder (SUD):
  - Antisocial personality
  - Mood disorders
  - Anxiety disorders
- In SUD samples, more than half would experience an Axis I or II disorder in their lifetime.

# Psychopathology

- Psychopathology as a risk factor
  - Self-medication
- Psychiatric symptoms may result from chronic intoxication
- Long-term substance use can lead to psychiatric disorders that may not remit

# Psychopathology

- Substance abuse and psychopathological symptoms may be meaningfully linked.
- The SUD and psychiatric disorder are unrelated
- Typically require treatment of both
  - Exception: those with temporary symptoms of a substance-induced disorders

# Other Theories

- Psychopathology may interfere with an individual's judgment or ability to appreciate consequences
- Psychopathology may accelerate the process of substance dependence
- Psychopathology may reinforce the social context of drug use

# Diagnosis

- Can be a complicated process
- Routine screening:
  - History of trauma
  - Family history
  - Symptomatology
  - Client's safety and suicide
  - Cognition

# Diagnosis

Rules and guidelines:

- Length: 4 weeks of abstinence
- If the symptoms are qualitatively or quantitatively not what one would expect, given the amount and duration of the substance use

# Treatment

- A heterogeneous group
- Sequential, parallel, and integrated treatment models

# Treatment

- General principles:
  - Empathy
  - Assist to set goals
  - Educate
  - Monitor symptoms
  - Monitor adherence
  - Assist to develop skills
  - Have available resources
  - Reinforce
  - Expect occasional lapses

# Anxiety Disorders

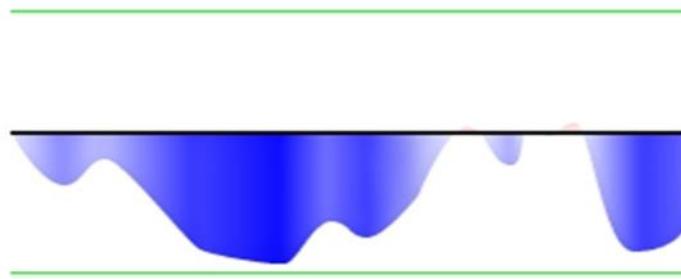
- Difference between fear and anxiety
- Anxiety: a usually neglected presentation in psychiatric disorders

# Generalized Anxiety Disorder

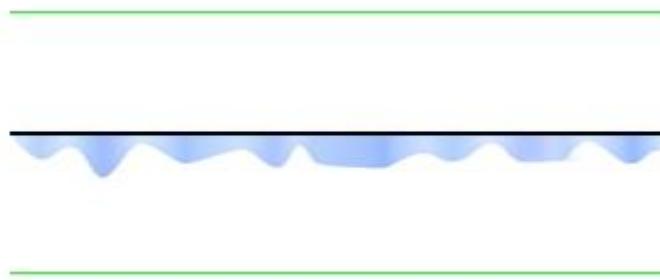
- Excessive anxiety and worry (apprehensive expectation), occurring more days than not for at least 6 months.
- The person finds it difficult to control the worry.
- The anxiety and worry are associated with three or more of the following six symptoms (with at least some symptoms present for more days than not for the past 6 months):
  - Restlessness or feeling keyed up or on edge
  - Being easily fatigued
  - Difficulty concentrating or mind going blank
  - Irritability
  - Muscle tension
  - Sleep disturbance (difficulty falling or staying asleep, or restless unsatisfying sleep)

# Depressive Disorders

- Major Depressive Disorder



- Dysthymia



# Depressive Episode

- Five or more of the following A Criteria (at least one includes A1 or A2)
  - A1 Depressed mood—indicated by subjective report or observation by others (in children and adolescents, can be irritable mood).
  - A2 Loss of interest or pleasure in almost all activities— indicated by subjective report or observation by others.
  - A3 Significant (more than 5 percent in a month) unintentional weight loss/gain or decrease/increase in appetite (in children, failure to make expected weight gains).
  - A4 Sleep disturbance (insomnia or hypersomnia).
  - A5 Psychomotor changes (agitation or retardation) severe enough to be observable by others.
  - A6 Tiredness, fatigue, or low energy, or decreased efficiency with which routine tasks are completed.
  - A7 A sense of worthlessness or excessive, inappropriate, or delusional guilt (not merely self-reproach or guilt about being sick).
  - A8 Impaired ability to think, concentrate, or make decisions— indicated by subjective report or observation by others.
  - A9 Recurrent thoughts of death (not just fear of dying), suicidal ideation, or suicide attempts

# Major Depressive Disorder

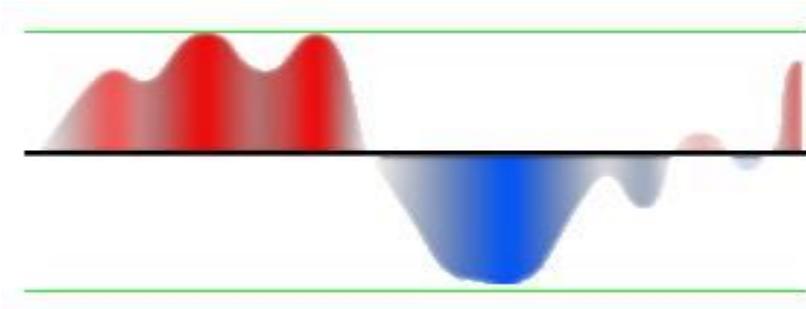
- The symptoms cause clinically significant distress or impairment in social, occupational, or other important areas of functioning.
- The symptoms are not due to the direct physiological effects of a substance (e.g., drug abuse, a prescribed medication's side effects) or a medical condition (e.g., hypothyroidism).
- There has never been a manic episode or hypomanic episode.
- MDE is not better explained by schizophrenia spectrum or other psychotic disorders.
- The symptoms are not better accounted for by bereavement.

# Dysthymia (Persistent Depressive Disorder)

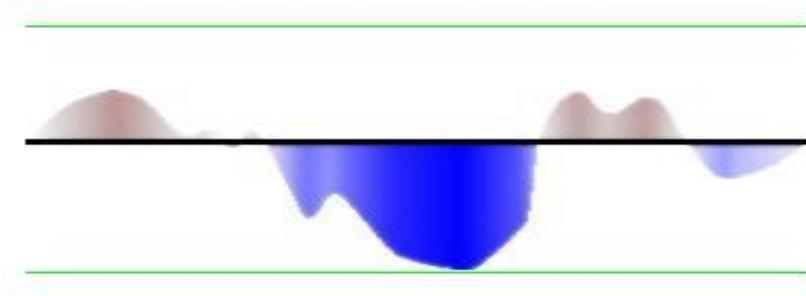
- Depressed mood for most of the day, for more days than not, as indicated by subjective account or observation by others, for at least 2 years.
- Presence while depressed of two or more of the following:
  - Poor appetite or overeating
  - Insomnia or hypersomnia
  - Low energy or fatigue
  - Low self-esteem
  - Poor concentration or difficulty making decisions
  - Feelings of hopelessness
- During the 2 year period of the disturbance, the person has never been without symptoms from the above two criteria for more than 2 months at a time.
- The disturbance is not better accounted for by MDD or MDD in partial remission.

# Bipolar Mood Disorder

- Bipolar I Disorder



- Bipolar II Disorder



# Manic Episode

- A. A distinct period of abnormally and persistently elevated, expansive, or irritable mood, lasting at least 1 week (or any duration if hospitalization is necessary).
- B. During the period of mood disturbance, three (or more) of the following symptoms have persisted (four if the mood is only irritable):
  - inflated self-esteem or grandiosity
  - decreased need for sleep (e.g., feels rested after only 3 hours of sleep)
  - more talkative than usual or pressure to keep talking
  - flight of ideas or subjective experience that thoughts are racing
  - Distractibility
  - increase in goal-directed activity (either socially, at work or school, or sexually) or psychomotor agitation
  - excessive involvement in pleasurable activities that have a high potential for painful consequences (e.g., engaging in unrestrained buying sprees, sexual indiscretions, or foolish business investments)

# Bipolar Depression

- Early age at onset
- Psychotic depression (esp before age 25)
- Post-partum depression (esp with psychotic features)
- Bipolar family history
- Cyclicity (onset, duration, frequency)
- Atypical, seasonal
- Psychomotor retardation (or even extreme agitation)
- Mixed features

# Psychotic Disorders

- Characteristic symptoms (Criterion A): Two (or more) of the following, each present for a significant portion of time during a 1-month period (or less if successfully treated):
  1. Delusions
  2. Hallucinations
  3. Disorganized speech (e.g., frequent derailment or incoherence)
  4. Grossly disorganized or catatonic behavior
  5. Negative symptoms (i.e., affective flattening, alogia, or avolition)

# ADHD

- Inattention
  - a. often fails to give close attention to details or makes careless mistakes in schoolwork, work or other activities
  - b. often has difficulty sustaining attention in tasks or play activity
  - c. often does not seem to listen when spoken to directly
  - d. often does not follow through on instructions and fails to finish schoolwork, chores or duties in the workplace
  - e. often has difficulty organizing tasks and activities
  - f. often avoids, dislikes, or is reluctant to engage in tasks that require sustained mental effort
  - g. often loses things necessary for tasks or activities
  - h. is often easily distracted by extraneous stimuli
  - i. is often forgetful in daily activities

# ADHD

- Hyperactivity/Impulsivity
  - a. often fidgets with hands or feet or squirms in seat
  - b. Often leaves seat in situations when remaining seated is expected
  - c. often runs about or climbs excessively in situations in which it is inappropriate
  - d. often has difficulty playing or engaging in leisure activities quietly
  - e. is often "on the go" or often acts as if "driven by a motor"
  - f. often talks excessively
  - g. often blurts out answers before questions have been completed
  - h. often has difficulty awaiting turn
  - i. often interrupts or intrudes on others

# Behavioral Addictions

- Eating Disorders
- Sex Addiction
- Pathological Gambling
- Internet Gaming Disorder

# Pharmacotherapy

- Major depression
  - Efficacy comparable to depression alone group
  - 1 week abstinence
  - Rate of sustained abstinence
- Bipolar disorder
  - Mood stabilizers

# Pharmacotherapy

- Schizophrenia and other psychotic disorders
  - Potential benefit of second-generation antipsychotic medications
- Anxiety disorders
  - Benzodiazepine controversy
- Attention Deficit Hyperactivity Disorder (ADHD)
  - Stimulant controversy
  - Bupropion for adult ADHD and cocaine abuse
  - Venlafaxine in patients with ADHD and alcohol use disorder

# Pharmacotherapy

## Medications with abuse potential

- Preparation which limit potential for abuse
- Objective measures for improvement
- Monitoring substance use
- Monitoring prescriptions

# Pharmacotherapy

- Targeting substance dependence in dually diagnosed patients
  - Disulfiram may cause or exacerbate psychosis
  - Naltrexone may improve drinking outcomes in patients with alcohol dependence and schizophrenia

# Psycho-social Interventions

## Cognitive Behavioral Therapy (CBT)

- additional techniques include the identification of cognitive distortions associated with both disorders
- identifying meanings of substance use in the context of disorder
- teaching new coping skills

# Psycho-social Interventions

## Motivational Interviewing

- a brief treatment conducted in as few as two sessions, sometimes aimed at helping the patient accept other psychotherapy (e.g., CBT)
- The transtheoretical *stages-of-change model* describes a sequential process of five stages of change in recovery for patients with SUDs: precontemplation, contemplation, preparation, action, and maintenance.

# Psycho-social Interventions

## Contingency Management

- Systematic use of reinforcement
- reinforce behavior that meets specific, clearly defined, and observable goals such as abstinence, medication adherence, therapy attendance, or completion of treatment goals

## Self-help Groups

# Case 1

- A 34 year old male patient, with irritability and aggression, is referred to the emergency believing that the Intelligence Service has put cameras and microphones in his room. The symptoms have emerged following increased use of methamphetamine in the past month.

## Case 2

- A 23 year old female university student, referred to you with poor grades at the university. During interview, she mentions that she can no longer enjoy from life and has though about ending her life. She has gained weight and has slept poorly. In history, she states she has used cannabis since college years and has increased the dose and frequency of cannabis recently.

Thanks

# **Assessment, Diagnosis, and Treatment Planning**

## **in Patients with OUD**

**BY:**

**Dr M.J.MORABBI .MD. Addiction Studies PHD**

# Aims:

**Increasing knowledge and clinical skills development in**

- **Assessment of patients with opioids use disorder**
- **Diagnostic criteria for opioids use disorder**
- **Treatment planning**

**Assessment is the process of obtaining information about the patient's drug use and how it is affecting his or her life. It is an essential part of treatment and care for people who use drugs.**

**before commencing the assessment, it is important to do  
three things :**

**Is the patient able to complete the assessment?**

# Acute conditions

- Some patients might present **in acute distress** in the emergency room
- Usually difficult to take a good medical history, so get a **prompt physical and psychiatric assessment and diagnosis.**
- **Symptom oriented treatment** with continuing monitoring until Symptoms resolve. Usually, most symptoms will resolve within few hours in the emergency room setting.

## **Establish rapport with the patient**

- spend a few minutes on ‘**small talk**’.

( Introduce yourself, and ask the patient for his or her name.)

- **open-ended question**
- **show the patient empathy**

**Explain the assessment process to the patient.**

**Assurance the patient that the assessment is confidential.**

**Before you begin the assessment, ask the patient if he or she  
has any questions for you.**

# **Principles of Patient's Assessment**

- Privacy
- Confidentiality
- Empathy
- Multidimensionality And comprehensiveness

# AREAS OF ASSESSMENT

- Demographic characteristics
- Drug use history
- History of drug treatments
- High risk behaviors
- Physical health status
- Psychiatric health status
- Legal problems
- Employment
- Family problems

# **Demographic characteristics**

- **Age**
- **Gender**
- **Education level**
- **Marital status**

- **Female patients** should be asked if they are pregnant and offered the opportunity to take a pregnancy test.

# **Substance Use History**

# General instructions

- To list common substances of use
- Age of initiation
- Years of regular substance use
- Days of use during last month
- Route of administration
- Amount of use in a typical day of use

- Last episode of drug use
- Have you ever overdosed?
- Have you ever experienced withdrawal symptoms in the past?

# **Route of administration**

**1.oral ingestion**

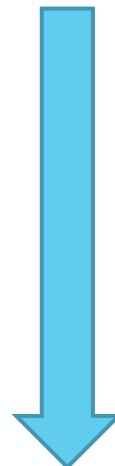
**2.Sniffing/snorting**

**3.Smoking/inhalation**

**4.Non IV injection**

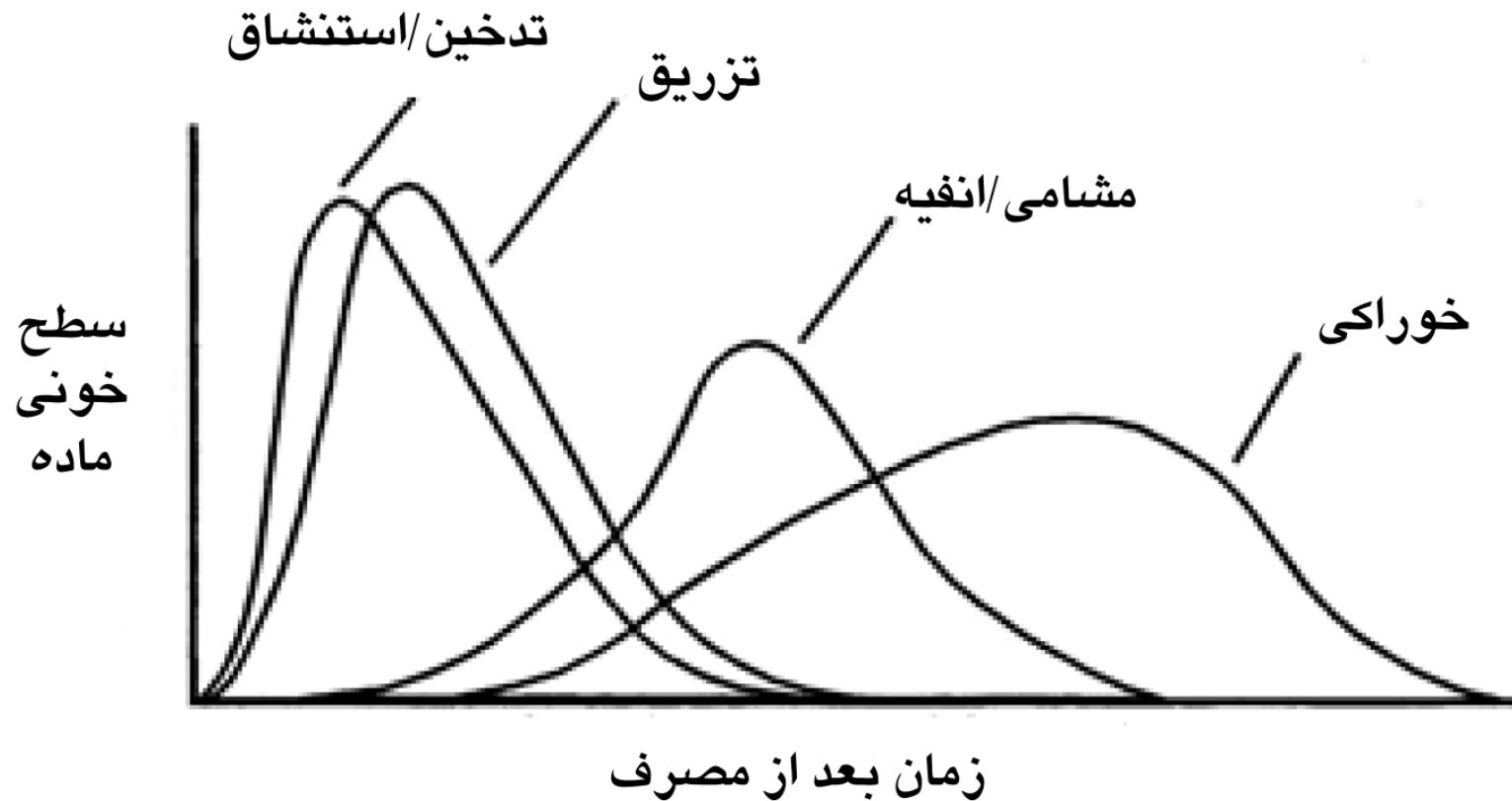
**5.IV injection**

**Lower risk**



**Higher risk**

# Time to peak serum levels by route of administration



If patient reports using a drug via ***more than one route***

write ***the route with highest risk*** and bring other routes in the  
comment column.

- **Amount of use in a typical day of use**
  - **Main problematic drug of use**
  - **Could be more than one drug**

## **Risk Behaviors :**

- **High risk drug use**
- **High risk sexual behavior**

## ➤ High risk drug use

- Injecting drug use
- Reuse of own syringe
- Sharing syringes:
  - Borrowing a syringe used by other people
  - Lending your own syringe to others

if the patient **inject** a drug, ask about injecting behaviours:

- Have you ever used a needle or syringe after some one else has used it?
- Do you have any infections or sores around where you inject?
- Have you been tested for **HIV, hepatitis C or hepatitis B?**

# **High risk sexual behavior**

- **Unprotected sexual behavior**
- **Having multiple partners**
- **Sex after using methamphetamine or other drugs**  
**(Sex drug link)**
- **Sex exchange drug or money**

# Treatment History

If the patient indicates they have previously *experienced withdrawal symptoms*, ask:

- *What symptoms* did you experience?
- What did you do or *what medications* did you take to relieve these symptoms?
- Did you experience any *serious complications* such as seizures or hallucinations?
- Do you have *any concerns* about your withdrawal?

# **Physical Health**

# History of medical diseases

- Attend to *any physical complaint*
- Check history of *medical disease*
- Common medical disease according to demographic characteristics
- Common *medical disease among people who use/inject* drugs

HIV/HCV/HBS testing/TSI

## **Ask the patient if they have any history of, or currently have:**

- ***Seizures*** or epilepsy
- Diabetes
- Heart disease
- Liver disease
- Viral hepatitis
- Tuberculosis
- Head injury
- Physical or intellectual disability (note type of disability)
- ***Allergies to any medications***
- Any prescribed or over-the-counter ***medications they are currently taking***

# **Psychiatric Health**

**Many people who use drugs have poor mental health.** Ask the patient:

- Have you ever been diagnosed with **schizophrenia**?
- Have you ever been diagnosed with depression or **bipolar disorder**?
- Have you ever been diagnosed with **post-traumatic stress disorder**?
- Have you ever been diagnosed with any other mental health problem?
  - Have you ever been given medication for a mental illness?
  - Have you ever deliberately hurt yourself or tried to kill yourself? Do you feel like you may try to hurt or kill yourself?

## **Schizophrenia**

Symptoms appear before heavy substance use.

Symptoms persist despite drug abstinence.

More likely to have a family history of psychotic disorders.

Antipsychotics markedly improve symptoms.

Often present with bizarre delusions, auditory hallucinations and/or thought disorder.

Poorer insight into their psychosis.

## **Drug Induced psychosis**

Symptoms appear only during periods of heavy substance use/sudden increase in potency.

Symptoms abate or are reduced with drug abstinence.

Less likely to have a family history of psychotic disorders.

Antipsychotics typically do not improve symptoms.

Often present with non-bizarre delusions and/or visual hallucinations.

Better insight into their psychosis.

- If there are only some symptoms rather than the full criteria, then a substance-induced etiology may be more likely.
- in 35 to 40 per cent of cases, it may be impossible to determine if a mood disorder is primary or substance-induced.

- Co-morbid psychiatric disorders generally have greater severity of symptoms, are more resistant to treatment and have an increased relapse rate.

**Men use substances more often than women, making them more likely to have substance-induced psychiatric symptoms. Women using substances are more prone to an accelerated progression, or telescoping, to the development of SUD and admission to treatment with higher rates of comorbid primary psychiatric disorders, especially mood, anxiety and eating disorders.**

# Psychologic and psychiatric treatments

- **History of receiving psychosocial treatments/counselling**
- **History of psychiatric visit**
- **History of admission in psychiatric ward**
- **Psychiatric medications**
  - 
  - Lifetime**
  - 
  - Last month**

**The clinical assessment of persons with SUD also requires screening for non-suicidal self-injurious behavior, suicidal behavior and potential for violence/aggression.**

## **Legal, Employment and Familial Functions**

## **Diagnostic criteria for opioids use disorder**

## **From Use to Use Disorder**

- Opioids use is commonly initiates with opium or prescription opioids (e.g., tramadol) recreationally.
- Recreational use escalates over time, with more frequent episodes of use, increasing amounts per episode, and changes in the route of administration to deliver faster effects (iv)
- Inability to control use
- Impairment in many areas of functioning (relationships, social function, and may develop work, housing, and legal problems

# **DSM 5 opioids Related Disorders**

- Opioids Use Disorder
  - Opioids Intoxication
  - Opioids Withdrawal
  - Other Opioids Induced Disorders
- (included in the classification of that disorder class)
- Depressive
  - Anxiety
  - Sexual dysfunction
- Delirium

## ➤ **Loss of Control**

- taken in larger amounts or over longer period
- persistent desire or unsuccessful efforts to cut down or control use
- much time spend in activities to obtain, use, or recover from use
- craving, strong desire, or urge to use

## **Social Problems**

- failure to fulfil major obligations at work, school, or home
- continuing use despite persistent/recurrent social or interpersonal problems
- Important social, occupational, or recreational activities are given up or reduced

## Risky Use

- use in situations in which it is physically hazardous
- use continues despite persistent/recurrent physical or psychological problems

## **Physiological effects**

tolerance

withdrawal

## **Criteria count as severity indicator**

- Mild ( 2-3)
- Moderate ( 4-5)
- Severe ( 6-11)

# Treatment Planning

- Patient's motivation and readiness for treatment
- Patient's experience with different treatment methods
- Patient's understanding and expectation from treatment

Developing a treatment plan *involves reviewing the patient's assessment* and *consulting with the patient* as necessary.

The patient **has the right to be involved in making decisions** about what treatment he or she receives, and involving the patient can help to improve patient cooperation with treatment.

The treatment plan should be developed using the ***stepped care approach***.

Stepped care involves matching treatment to patients based on the **least intensive intervention that is expected to be effective**. Based on how the patient responds to the chosen intervention, the healthcare worker *can increase* ('*step up*') or *reduce* ('*step down*') the intensity of treatment.

Once a treatment plan has been commenced, it is important to  
regularly evaluate the patient's progress and determine if the  
interventions that were used have been useful to the patient.

# Stages of change

- Precontemplation
- Contemplation
- Preparation
- Action
- Maintenance
- Relapse

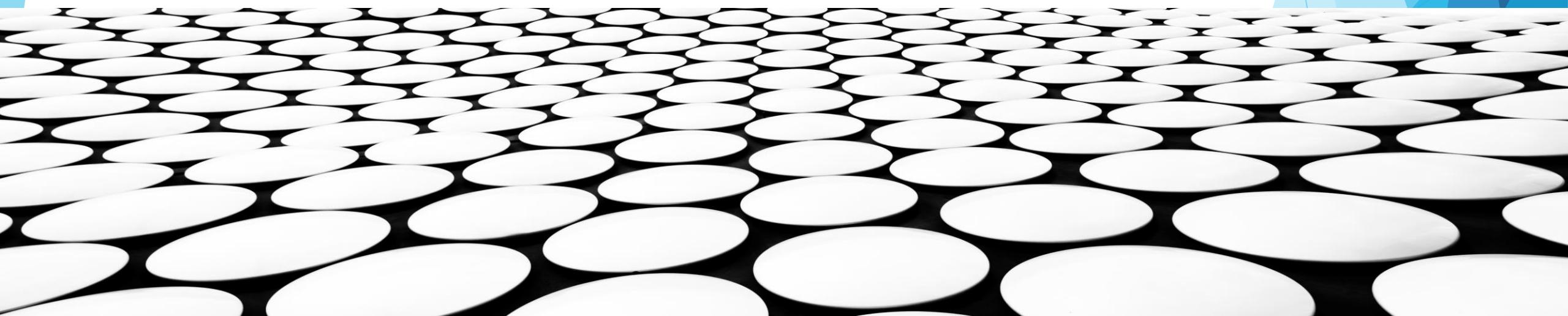
# Precontemplation

- Does not see themselves as having a problem although others might identify the problem.
- No intention of changing the problem and don't want to hear about it.
- Desire to change the people around them
- Often seen as resistant or “in denial”

**I don't have a problem**

# Contemplation

- Recognizes that there is *some reason for concern*.
- Seesaws between *reasons to change and reasons to stay the same*.
- Is best *pictured by a scale*, you've the argument to change your position and the argument to stay at your position and they *almost in equal balance*.



# Continue.....

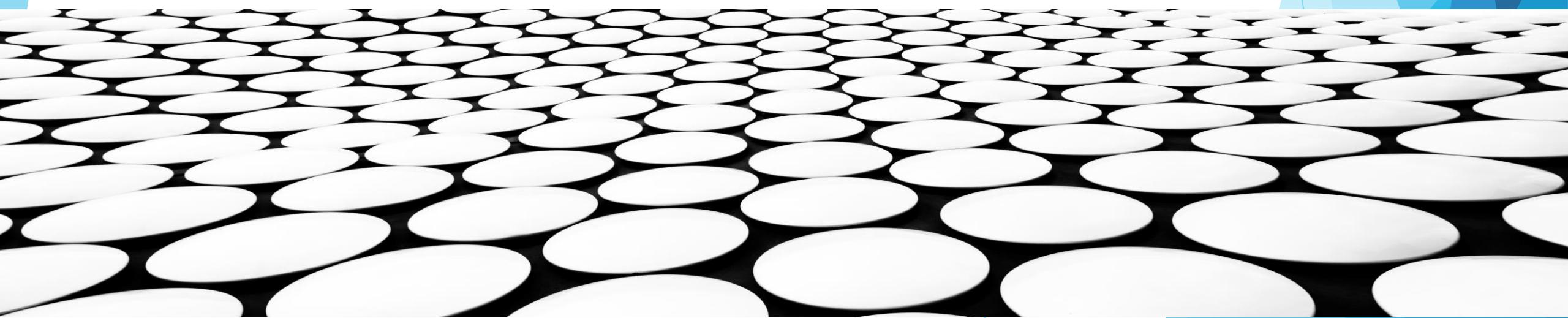
- Characterized *by ambivalence* – both considers and rejects change
- Stuck
- The **but stage**
- Indefinite plan to change in *next 6 months*
- Can spend years here
- *Fear of failure*

*I have a problem, but .....*

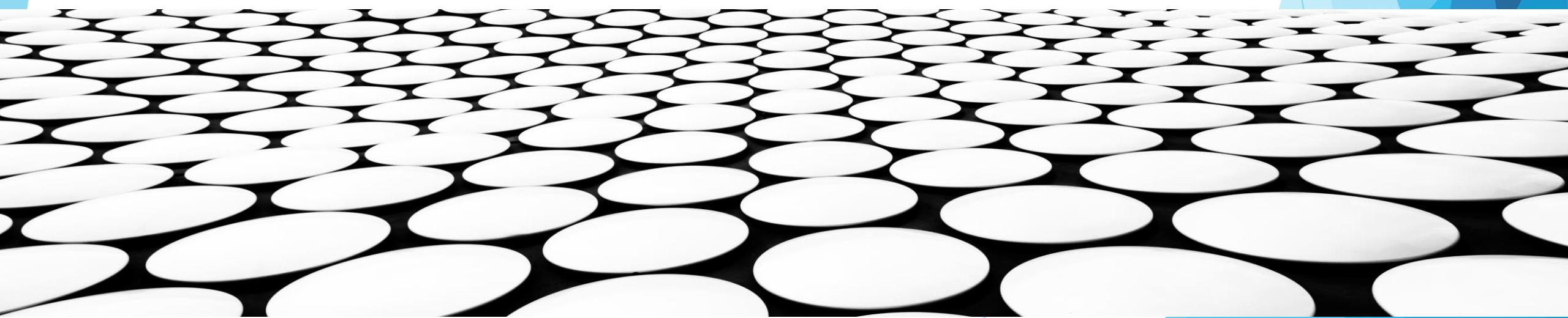
# Preparation

- Plan to change in the next month.
- Small changes may actually be happening here.

I'm making a plan to resolve my problem.



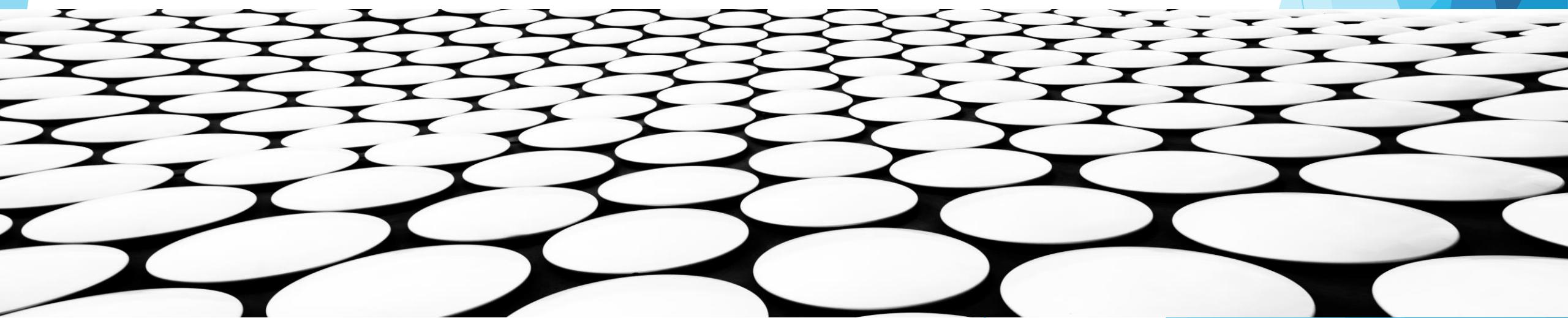
**rather than diving in headfirst they usually just test the waters.**



# Action

- person is engaging in particular actions to bring about change.
- Visible change happens.
- It's usually very difficult.

*I'm working on it and it's very difficult.*



# Relapse

- A reversion back to problem behavior.
- Any movement backwards through the cycle.
- Usually involves going back to contemplation.
- Not necessarily a bad thing.(reevaluate and make small changes in quit plan)
- Is to be expected(Behavior Changing take many *tries* to succeed)

*I messed up and .....*

## *Important points:*

1. Stage of change constantly is changing.
2. Pushing forward will result in resistance.
3. People are in different stages for different issues.
  - Precontemplation about opium use
  - Contemplation about Methamphetamine use
  - Preparation about cigarette smoking

# Effectiveness of MMT and BMT

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TEHRAN UNIVERSITY  
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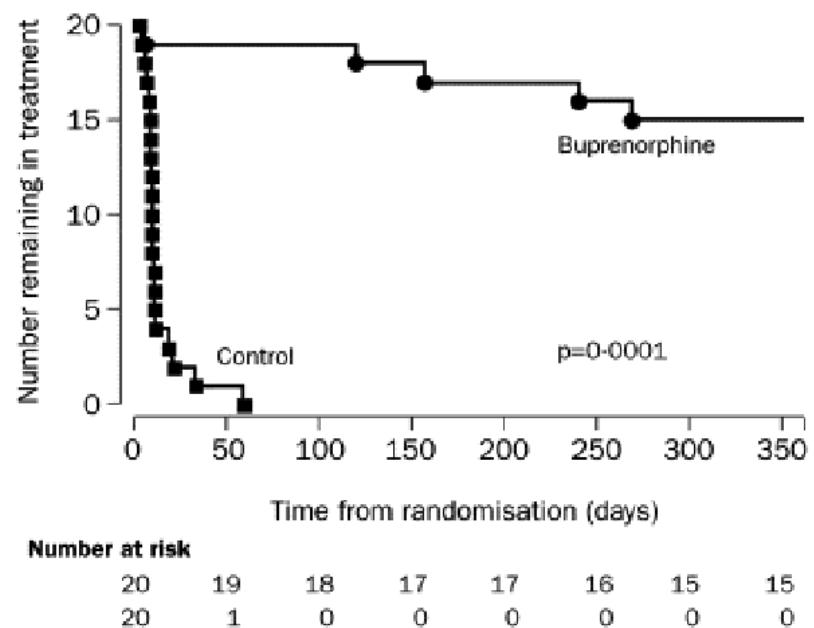
# Retention in Treatment

Methadone helps reduce **cravings** and **withdrawal** symptoms, making it easier for individuals to remain committed to their treatment plan. Research shows that MMT is associated with improved **retention** rates in substance use disorder programs, primarily because methadone acts as a long-acting opioid agonist, stabilizing patients and allowing them to avoid the immediate highs and lows associated with short-acting opioids..

Buprenorphine, as a partial opioid agonist, helps manage **withdrawal** symptoms and **cravings** with a **lower risk of producing euphoria** compared to full agonists. This reduces the potential for misuse and supports a stable transition away from dependence on stronger opioids. Studies indicate that BMT is associated with increased **retention** in treatment programs, as it provides a **safer** and controlled pathway for patients, helping them to stay motivated and engaged in both medical and counseling aspects of their recovery.

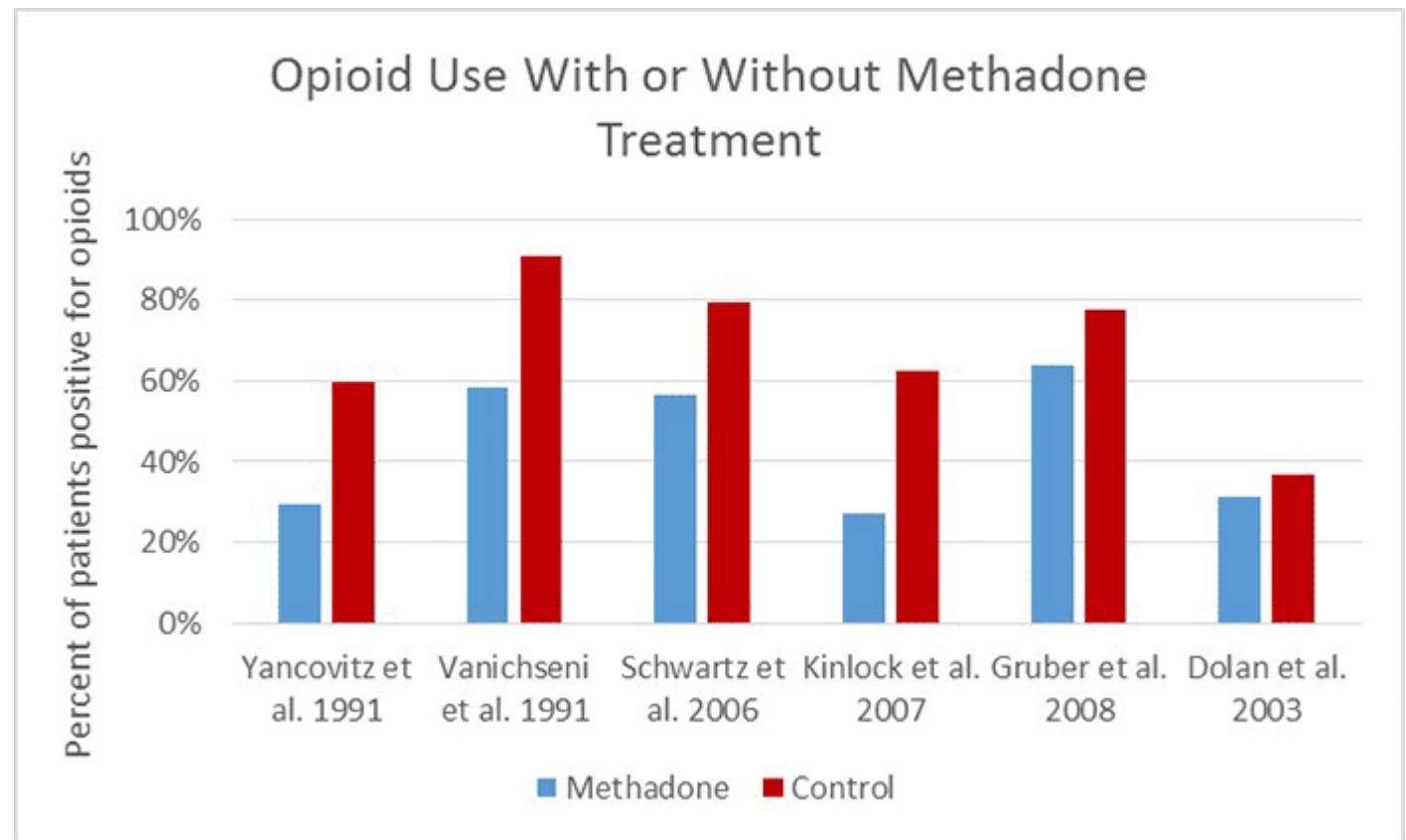
# Stay in Treatment

A Swedish study compared patients maintained on 16 mg of buprenorphine daily to a control group that received buprenorphine for detoxification (6 days) followed by placebo.



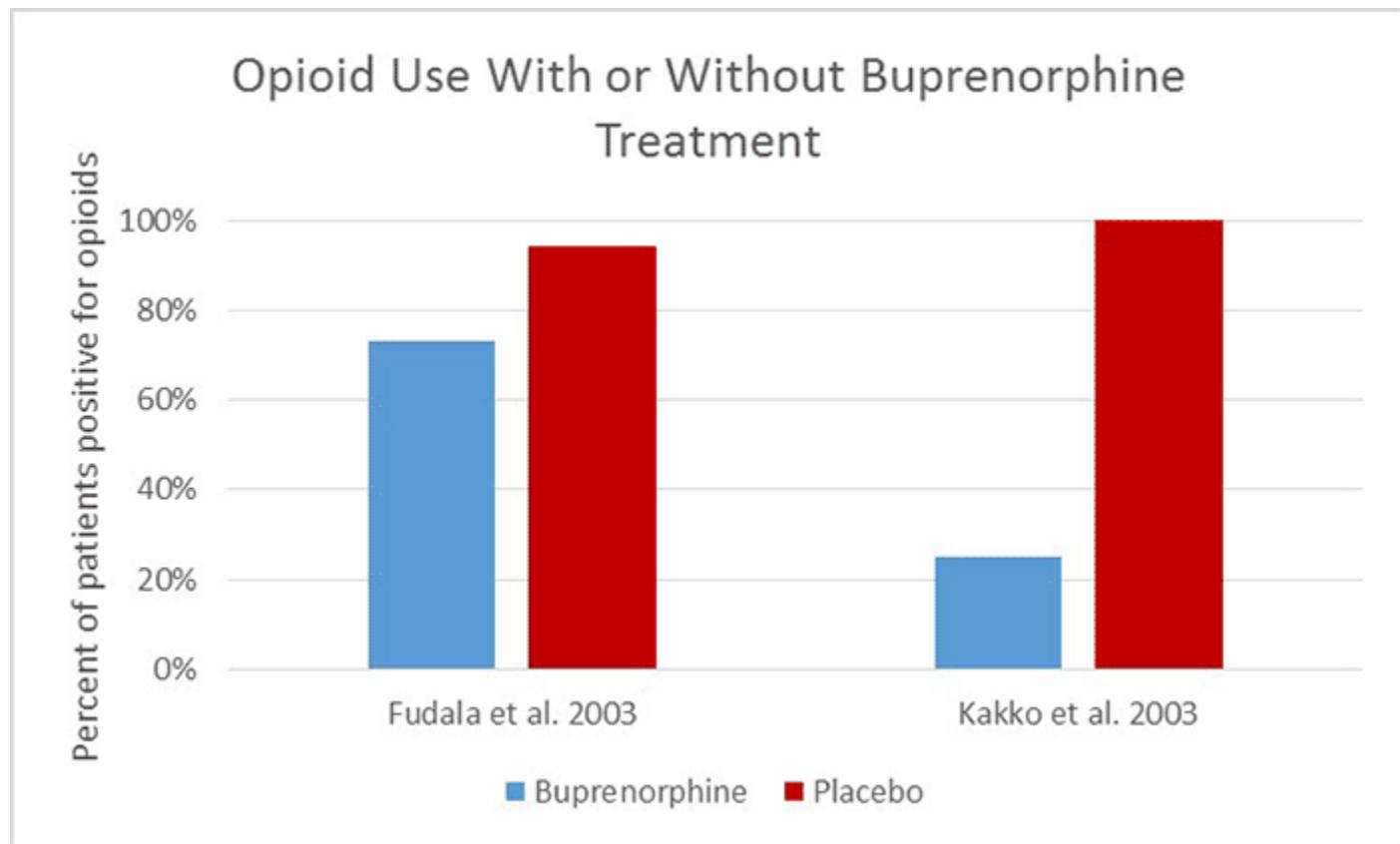
# Illicit Drug Use

Methadone Maintenance Treatment (MMT) and Buprenorphine Maintenance Treatment (BMT) are widely recognized as effective strategies for reducing illicit drug use among individuals with opioid dependence. Both treatments work by mitigating withdrawal symptoms and cravings, allowing individuals to stabilize their lives without experiencing the highs and lows of opioid misuse. MMT involves the daily administration of methadone, a full opioid agonist that prevents withdrawal symptoms by binding to opioid receptors in the brain, reducing cravings without inducing euphoria.



# Illicit Drug Use

Similarly, BMT uses buprenorphine, a partial agonist with a ceiling effect that limits euphoria and overdose risk, making it safer and appealing to a broader range of patients. Research has shown that both MMT and BMT significantly decrease illicit opioid use, reduce overdose rates, and improve overall health and social stability, though they may vary in effectiveness based on individual needs and treatment adherence.



# Reducing Diseases

- The effects of methadone and buprenorphine maintenance treatments (MMT and BMT) on reducing diseases like HIV and hepatitis C (HCV) are significant. Both treatments help decrease the need for injection drug use, which is a major transmission route for these infections. By managing withdrawal symptoms and reducing cravings, MMT and BMT lower the likelihood of risky behaviors such as needle sharing. Methadone, as a full opioid agonist, and buprenorphine, as a partial agonist, each provide a structured and safer alternative to illicit opioid use, stabilizing patients and reducing the frequency of injection.
- Additionally, maintenance treatment programs often include health screenings, counseling, and education on safe practices, which further contribute to a reduction in the transmission of HIV and HCV. Studies consistently show that individuals in MMT or BMT have a lower risk of contracting HIV and HCV, which not only benefits individual health but also has positive public health implications by reducing the overall transmission rates in the community.

# Reducing Crime

- The effects of methadone and buprenorphine maintenance treatments (MMT and BMT) on reducing **crime** rates are well-documented. Both treatments help individuals **stabilize** by managing opioid cravings and withdrawal symptoms, reducing the compulsion to engage in criminal activities to **fund drug use**. Studies show that individuals in MMT or BMT programs are less likely to be involved in **theft**, **drug-related offenses**, or other **illegal activities** often associated with substance dependence.

# Social Effect

- These treatments enable individuals to focus on **employment, education, and family responsibilities** without the disruptions of constant drug-seeking behavior. Many people in MMT and BMT report enhanced **quality of life**, improved **self-esteem**, and the ability to **rebuild relationships** that were strained by addiction. Moreover, the support often provided in these programs, such as counseling and peer support, contributes to long-term recovery and a better outlook for a stable, productive life free from the chaotic cycle of opioid dependence.



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## **Methadone maintenance therapy versus no opioid replacement therapy for opioid dependence (Review)**

Mattick RP, Breen C, Kimber J, Davoli M

# Introduction



Trusted evidence.  
Informed decisions.  
Better health.

Cochrane Database of Systematic Reviews

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- Methadone treatment is the **first widely used** opioid replacement therapy for heroin dependence and is utilized in many countries.
- The effectiveness of methadone as a maintenance treatment for opioid dependence has been **debated** compared to non-drug therapies.
- The aim of this study is to **evaluate the effects of methadone maintenance therapy** compared to treatments that do not involve opioid replacement.
- Previous research indicates that methadone can improve patient retention in treatment and reduce heroin use.
- Despite the widespread use of methadone, there are **still controversies** regarding its effectiveness, highlighting the need for further investigation.

# Method



Trusted evidence.  
Informed decisions.  
Better health.

Cochrane Database of Systematic Reviews

- The review focused on randomized controlled trials (RCTs) comparing methadone maintenance therapy with non-opioid replacement treatments such as detoxification and placebo medication.
- The inclusion criteria specified that participants must be individuals with opioid dependence, regardless of prior treatment history.
- Data extraction and analysis were conducted independently by two reviewers to ensure accuracy and minimize bias in evaluating the studies.
- The methodological quality of the included studies was assessed based on factors such as randomization procedure and allocation concealment to determine the risk of bias.
- A meta-analytic approach was employed to calculate pooled effect sizes for primary outcomes, including treatment retention and opioid use, providing a comprehensive synthesis of the results.

# Result



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- A total of eleven randomized controlled trials were included in the review, comprising 1,969 participants.
- Methadone maintenance therapy significantly improved retention in treatment, with relative risks (RR) ranging from 3.05 to 4.44 compared to non-opioid treatments.
- Participants receiving methadone had a lower rate of morphine-positive urine tests, with an RR of 0.66, indicating reduced heroin use.
- Self-reported heroin use was also significantly lower among those in methadone treatment compared to control groups.
- There was no statistically significant difference in criminal activity between the methadone group and non-opioid treatments, with an RR of 0.39.

# Result



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- The study found **no significant** impact of methadone on **mortality rates**, with an RR of **0.48**.
- The quality of evidence for retention and heroin use outcomes was rated as high, indicating **robust findings**.
- The studies included **varied in their settings**, comprising prisons, hospitals, and community-based treatments.
- Most studies reported **adequate dosing** of methadone, typically ranging from **60 mg to 100 mg per day**.

# Discussion



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- While methadone has been shown to decrease heroin use, the study highlights the need for **further research** to explore its impact on **criminal activity** and **mortality**, where no significant differences were observed.
- The review emphasizes the importance of **individualized treatment plans**, as factors such as **dosage** and the therapeutic relationship can influence treatment outcomes.
- Despite its effectiveness, the **ongoing controversy** surrounding methadone calls for continued evaluation of its role in opioid dependence treatment in **various populations** and settings.

# BMJ Open Methadone maintenance treatment programme reduces criminal activity and improves social well-being of drug users in China: a systematic review and meta-analysis

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Hua-Min Sun,<sup>1</sup> Xiao-Yan Li,<sup>1</sup> Eric P F Chow,<sup>2,3,4</sup> Tong Li,<sup>1</sup> Yun Xian,<sup>1</sup> Yi-Hua Lu,<sup>1</sup> Tian Tian,<sup>1</sup> Xun Zhuang,<sup>1</sup> Lei Zhang<sup>1,2</sup>

- The study found that methadone maintenance treatment (MMT) significantly reduced criminal activity among drug users in China.
- The self-reported arrest rate decreased from 13.1% at baseline to 3.4% and 4.3% after 6 and 12 months, respectively.
- Additionally, the rate of drug selling dropped from 7.6% to 1.9% and 3% after 6 and 12 months.
- Conversely, the employment rate and family relationships improved substantially, increasing from 26.4% to 59.8% and from 37.9% to 75% after 12 months of treatment.
- These findings highlight the effectiveness of MMT in enhancing the social and familial well-being of drug users in China.



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## **Buprenorphine maintenance versus placebo or methadone maintenance for opioid dependence (Review)**

Mattick RP, Breen C, Kimber J, Davoli M

# Introduction



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Buprenorphine maintenance treatment is recognized as an effective approach for managing opioid dependence.

Buprenorphine is a **partial agonist** that has weaker effects compared to methadone and heroin, potentially providing greater safety.

The use of buprenorphine can help **reduce illicit drug** use and increase the duration of treatment.

This study aims to evaluate the **efficacy** of buprenorphine compared to **placebo** and **methadone** in the management of opioid dependence.

# Method



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The review included randomized controlled trials comparing buprenorphine maintenance therapy to methadone maintenance therapy or placebo in individuals with opioid dependence.

Participants included those dependent on heroin or other opioids, with no distinctions made between users of heroin and those in methadone treatment prior to the study.

Buprenorphine maintenance was administered in doses above 1 mg, using various formulations such as sublingual tablets and implants.

Control interventions included methadone maintenance therapy with doses of 20 mg or higher or placebo, ensuring that all studies included a maintenance phase.

Primary outcome measures focused on treatment retention, opioid use (measured by urinalysis and self-reports), and other substance use, as well as criminal activity and mortality.

# Result



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The review included 31 trials with a total of 5,430 participants, showing varied quality of evidence from high to moderate.

Buprenorphine demonstrated significantly better retention in treatment compared to placebo at all doses examined, with a risk ratio of 1.50 for low doses.

High-dose buprenorphine ( $\geq 16$  mg) was shown to be more effective than placebo in suppressing illicit opioid use.

However, low- and medium-dose buprenorphine did not significantly suppress illicit opioid use compared to placebo.

Buprenorphine, when administered in flexible doses, was less effective than methadone in retaining participants in treatment, with a risk ratio of 0.83.

No difference between the buprenorphine and methadone groups were found for Criminal activity. For the other comparisons, no data on criminal activity were reported in the included studies.

# Discussion



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Buprenorphine is **effective** in retaining individuals in treatment for opioid dependence, particularly at **doses above 2 mg**, and can significantly reduce illicit opioid use at higher doses.

The results indicate that while **both medications can be effective**, methadone has a clear advantage in treatment retention, which is crucial for successful long-term outcomes.

**Other outcome measures** could be included in future studies, such as self-reported drug use, criminal activity, physical health, and psychological health, which were too **infrequently** and **irregularly** reported in the literature analyzed in the current review.

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## Articles



# Buprenorphine versus methadone for the treatment of opioid dependence: a systematic review and meta-analysis of randomised and observational studies

Louisa Degenhardt, Brodie Clark, Georgina Macpherson, Oscar Leppan, Suzanne Nielsen, Emma Zahra, Briony Larance, Jo Kimber, Daniel Martino-Burke, Matthew Hickman, Michael Farrell

# Introduction

- Opioid dependence, as defined by the ICD, involves a **cluster of symptoms** that include impaired control over opioid use, prominence of use of a substance in a person's life, and physiological symptoms including tolerance and withdrawal.
- **Fatal opioid overdose** is a major adverse outcome of extra-medical opioid use, as is **non-fatal overdose**.
- People who inject drugs are at risk of **HIV** and hepatitis C virus (**HCV**) infection, in addition to skin and soft tissue **infections** and infective **endocarditis**.
- Other outcomes associated with opioid dependence include **poorer quality of life**, **physical** and **mental** health problems, **criminal activity**, and involvement with the **criminal justice system**.

# Introduction

- Opioid agonist treatment (**OAT**) is an effective treatment for opioid dependence that reduces harms across multiple health outcomes.
- A range of opioids have been used in OAT, but the two most common are **buprenorphine** and **methadone**, both of which are included in the **WHO Model List of Essential Medicines**.
- There has been considerable discussion about whether and which of these two medications should be **preferred**, and in **which contexts**.
- Methadone is a **full opioid agonist** with no ceiling for respiratory depression, whereas buprenorphine is a **partial agonist** with a ceiling effect for respiratory depression at higher doses.

# Methods

- This study conducted a systematic review and meta-analysis in accordance with **GATHER** and **PRISMA** guidelines.
- Searches were performed in **MEDLINE**, **Embase**, **PsycINFO**, and **CENTRAL** from the inception of these databases until **August 1, 2022**.
- Randomized controlled trials (**RCTs**) and **observational** studies comparing buprenorphine and methadone treatment were included.
- The study population comprised adults (**aged  $\geq 18$  years**) with opioid dependence.
- **Primary outcomes** included treatment **retention** at various time points (1, 3, 6, 12, and 24 months). Treatment **adherence** and **extra-medical opioid use** were also examined.

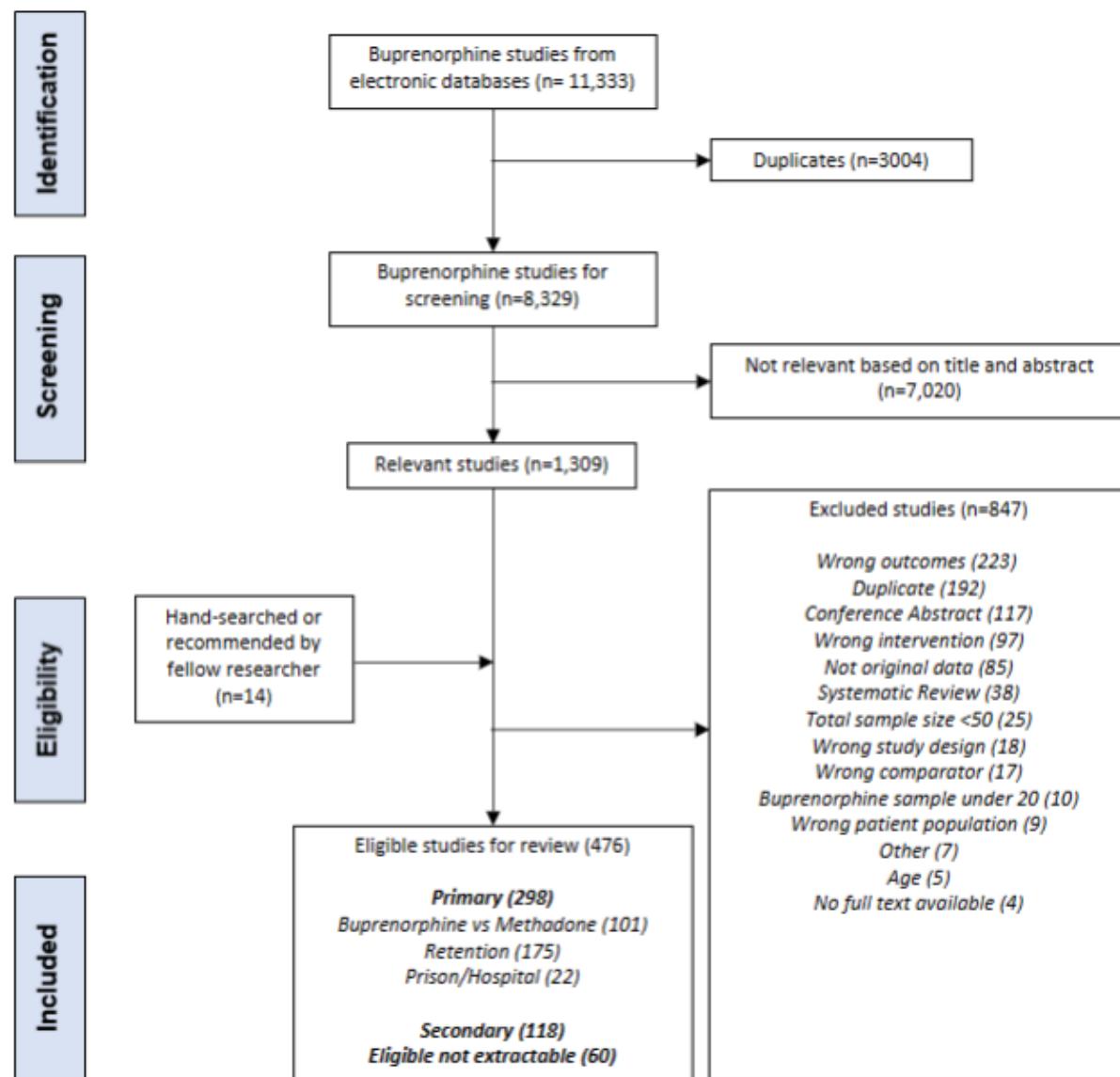
# Methods

- Secondary outcomes encompassed use of other drugs; opioid craving; precipitated withdrawal; criminal activity; engagement with the criminal justice system; mental health; non-fatal overdose; physical health; sleep quality; pain; global functioning, including treatment satisfaction; and adverse events.
- Data on study characteristics, participant details, and treatment received were extracted.
- Authors of the studies were contacted for additional data when required.
- Comparative estimates were pooled using random-effects meta-analyses.
- A total of 101 eligible studies were identified, comprising 32 RCTs and 69 observational studies.

# Methods

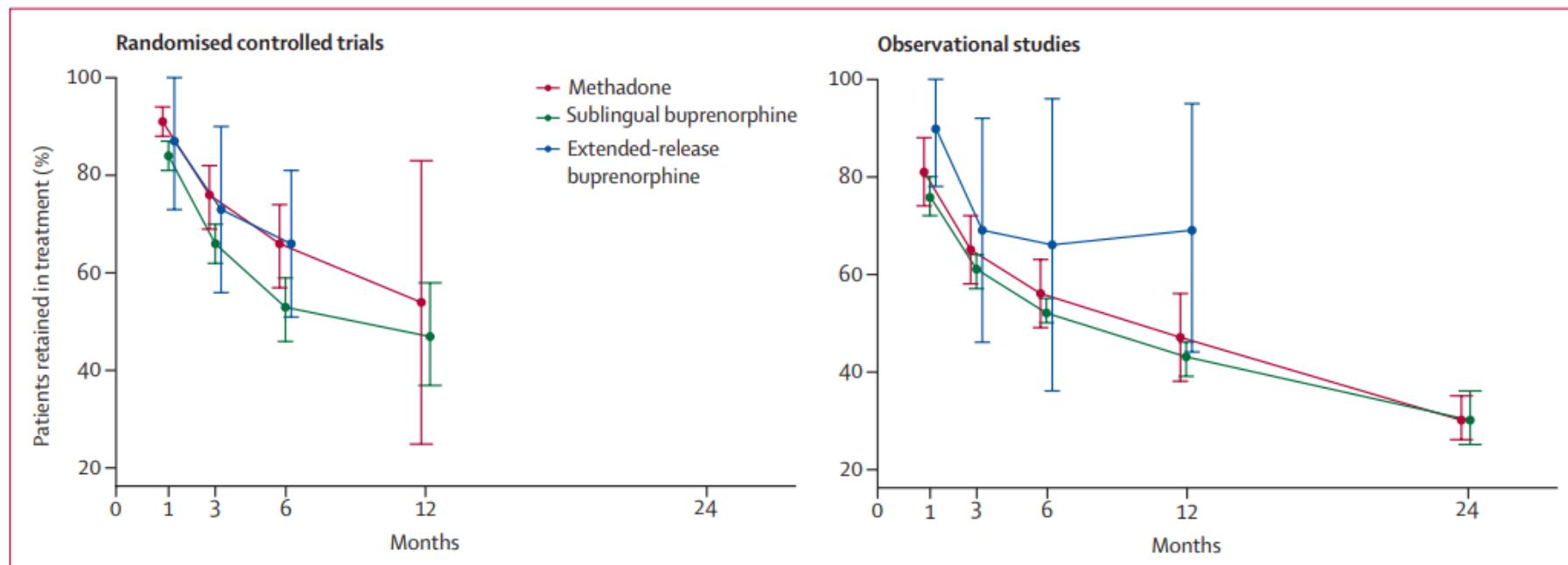
- A total of 1,040,827 participants were included in these primary studies.
- Inclusion criteria encompassed various treatment settings, including inpatient and outpatient facilities.
- Exclusion criteria were people younger than 18 years, trials exclusively including pregnant women and use of buprenorphine for detoxification.
- No restrictions were placed on language or publication type.
- Analyses included direct comparisons of risk ratios and standardized mean differences.
- This study is registered with PROSPERO (CRD42020205109).

Figure B1. PRISMA flow diagram



# Results

- At timepoints beyond 1 month, retention was better for methadone than for buprenorphine.
- Retention was generally higher in RCTs than observational studies.



**Figure 1: Retention in treatment with buprenorphine versus methadone at 1, 3, 6, 12, and 24 months**

Buprenorphine data are stratified by route of administration. Error bars are 95% CIs.

# Results

- There was **no evidence** suggesting that **adherence** to treatment differed with buprenorphine compared with methadone.
- There was some evidence that **extra-medical opioid** use was **lower** in those receiving **buprenorphine**.
- There was evidence of **reduced cocaine use, cravings, anxiety, and cardiac dysfunction** among people receiving **buprenorphine** compared with methadone.
- Evidence was found for **reduced hospitalization** in people receiving **methadone**.
- Buprenorphine was associated with **higher treatment satisfaction** compared with methadone.

# Discussion and conclusion

- There is consistent evidence across timepoints and study types that retention is better for methadone than buprenorphine after the first month of treatment.
- Few statistically significant differences between these treatments were identified for most other outcomes.
- Where differences were identified they were generally based on a small number of available studies and were not consistent across metrics and study types.
- This review highlights the importance of interventions to improve retention on opioid agonist treatment (OAT) as well as of harmonization of data collection for future evidence syntheses.

# Discussion and conclusion

- There is a need for **future studies** to expand evidence for many outcomes by standardizing measurement and reporting of outcomes.
- RCTs were often substantially **limited by small sample sizes** and low statistical power to detect differences between groups.
- **Observational** studies were constrained by the very high likelihood of **selection bias** and **confounding** due to probable differences in **characteristics of people** receiving buprenorphine compared with methadone.
- Future research could explore whether there are benefits for retention and other health outcomes in key **subpopulations** such as adolescents and older adults.
- The **limited data** on outcomes such as treatment **satisfaction** and **quality of life** demonstrate a need for patient-centred non-consumption outcomes to be included in future studies to investigate the **real-world effectiveness** of OAT.

# Naltrexone

## درمان با نالتrexون منطبق با پروتکل های وزارت بهداشت

Presented by:

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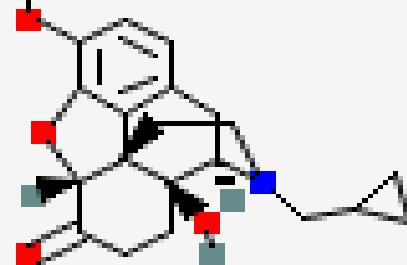
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# Naltrexone

- ▶ Synthesized in the 1960s
- ▶ Oral naltrexone was approved by FDA in 1984.
- ▶ Derivative from Noroxymorphone
- ▶ Noroxymorphone
  1. An opioid
  2. Metabolite of oxymorphone and oxycodone
- ▶ High affinity for  $\mu$ -opioid binding sites.
- ▶ lower affinity for the other receptors but can also reverse agonists at  $\delta$  and  $\kappa$  sites.

# Naltrexone

- Naloxone, Naltrexone, and Nalmefene are morphine derivatives with bulkier substituents at the N17 position.



Naltrexone



Morphine

# Naltrexone

- ▶ Reverses the effects of opioid analgesics.
- ▶ Inhibition of the typical actions of opioid analgesics, including analgesia, euphoria, sedation, respiratory depression, miosis, bradycardia, and physical dependence.
- ▶ Potential advantages (e.g., no abuse liability, no special regulatory requirements).

# Naltrexone

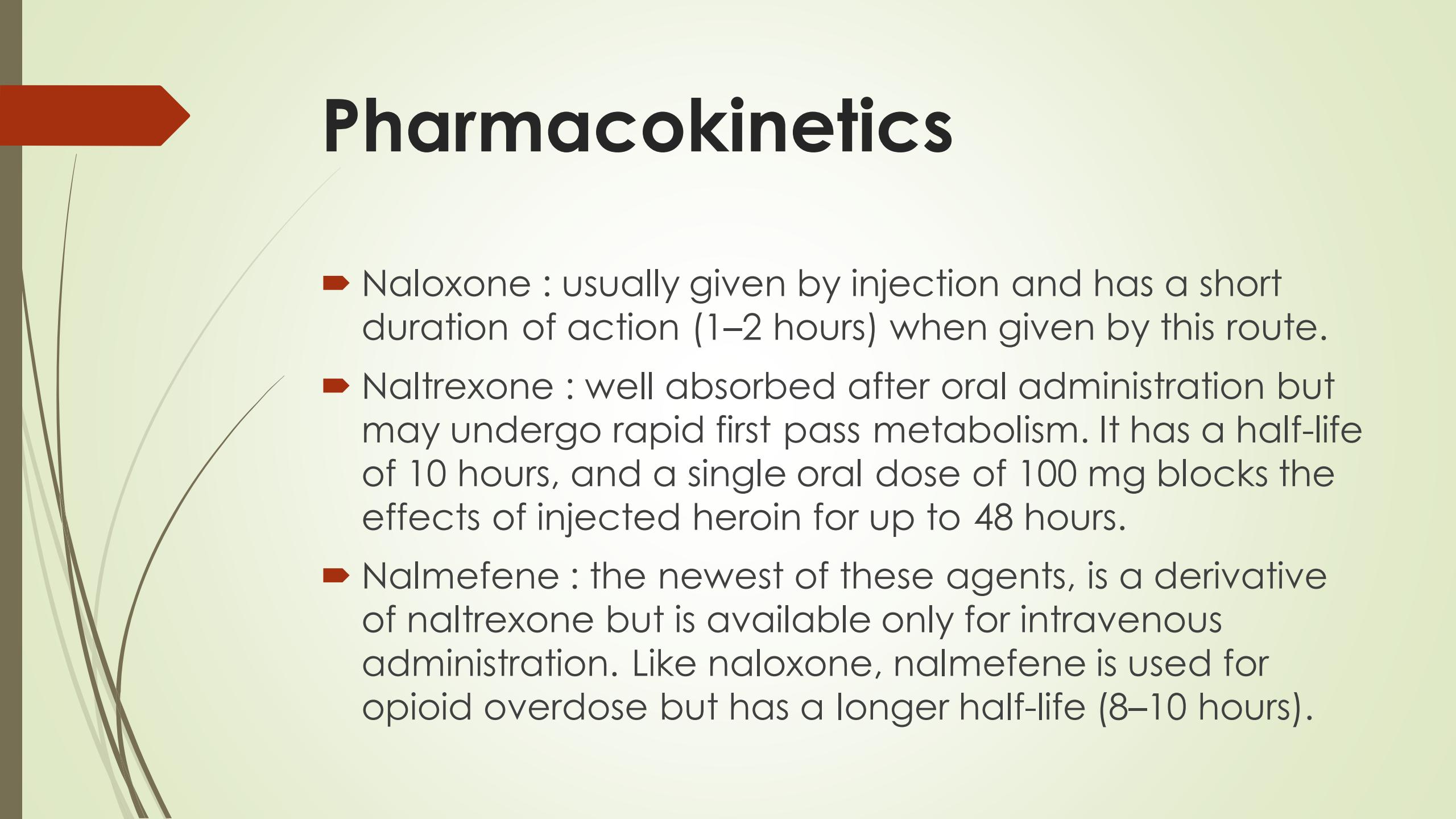
- Oral naltrexone is not widely used to treat opioid use disorder (OUD)
  1. Low rates of patient acceptance.
  2. Difficulty in achieving abstinence for the necessary time before initiation of treatment.
  3. High rates of medication nonadherence.
- A Cochrane review examined 13 randomized trials among 1,158 patients who were opioid dependent and provided counseling. The review concluded that oral naltrexone was not superior to placebo or to no medication in treatment retention or illicit opioid use reduction.

# Naltrexone

- ▶ Competitive mu-opioid receptor antagonist with strong receptor affinity.
- ▶ Does not activate the mu-opioid receptor and exerts no opioid effects.
- ▶ No alleviate withdrawal symptoms.
- ▶ No withdrawal when stopped.
- ▶ Cannot be diverted.
- ▶ If patients maintained on naltrexone use opioid agonists, naltrexone can block their effects.
- ▶ Because the interaction at the receptor is competitive, the blockade can potentially be overridden with high doses of opioids.

# Naltrexone

- ▶ After recent use of opioids can precipitate opioid withdrawal. Given its strong affinity, naltrexone can displace other opioids from the receptor.
- ▶ Patients must typically wait 7 to 10 days after their last use of short acting opioids and 10 to 14 days after their last use of long-acting opioids before taking their first dose of naltrexone.
- ▶ Oral: The gastrointestinal tract readily absorbs oral naltrexone. Peak concentrations occur in 1 to 2 hours.

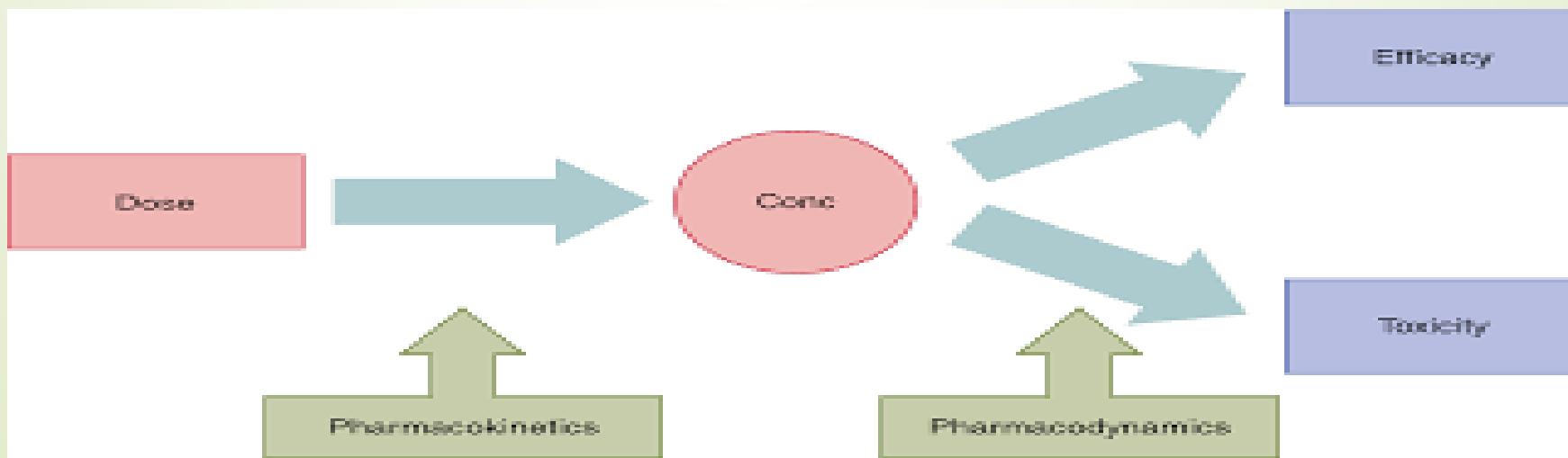


# Pharmacokinetics

- ▶ Naloxone : usually given by injection and has a short duration of action (1–2 hours) when given by this route.
- ▶ Naltrexone : well absorbed after oral administration but may undergo rapid first pass metabolism. It has a half-life of 10 hours, and a single oral dose of 100 mg blocks the effects of injected heroin for up to 48 hours.
- ▶ Nalmefene : the newest of these agents, is a derivative of naltrexone but is available only for intravenous administration. Like naloxone, nalmefene is used for opioid overdose but has a longer half-life (8–10 hours).

# Pharmacodynamics

- ▶ In individuals who are acutely depressed by an overdose of an opioid, the antagonist effectively normalizes respiration, level of consciousness, pupil size, bowel activity, and awareness of pain.
- ▶ There is no tolerance to the antagonistic action of these agents.



# درمان دارویی با نالترکسون ( پروتکل )

- 1-وقفه در تاثیر مواد افیونی بیمار را از رفتار موادجویانه دلسرد کرده و موجب رفع حالت شرطی نسبت به مواد افیونی می شود.
- 2-ضعف مدل درمان با نالترآسون فقدان سازوکاری است که شخص را به ادامه مصرف وادار کند.
- 3-در عمل بدون پیگیری بیمار و توضیح و تشویق درمانگر و خانواده بسیاری از معتادان مدت کوتاهی پس از ترک مصرف مداوم نالترکسون را ادامه می دهند.
- 4-صرف نالترکسون با تغییرات عمدۀ خلقي یا سایر اختلال هاي روانی همراه نیست. عوارض عمدۀ جسماني نیز گزارش نشده اند.
- 5-موفقیت درمان نالترکسون با عوامل اجتماعی مانند تحصیلات، شغل، تأهل، انگیزه بالا، حمایت خانوادگی و اجتماعی و ادامه درمان پیشگیرانه از عود ارتباط دارد.
- 6-با توجه به حمایت خانواده در ایران و به خصوص نظارت خانواده بر مصرف منظم دارو به نظر می رسد احتمال موفقیت با این روش درمانی نسبت به کشورهای غربی بیشتر باشد.

# پیش از آغاز درمان با نالترکسون ( پروتکل )

1- فواید و ضرورت درمان با نالترکسون را برای پیشگیری از عود.

2- ارتباط مستمر با پزشک و جلسات ویزیت منظم .

3- شروع درمان نیازمند سمزدایی کامل است و نباید پیش از آن تجویز شود، زیرا با علایم شدید ترک همراه است.

4- انجام تستهای کبدی ( علت هپاتیت ویروسی یا سوءصرف الکل )

# آغاز درمان با نالترکسون ( پروتکل )

1- حصول اطمینان از سمزدایی کامل بیمار.

2- اگر هنوز گیرنده های افیونی با مواد افیونی اشغال شده باشند، بیمار با علایم شدید ترک مواجه می شود که تا سه روز می تواند ادامه پیدا آند.

3- در مورد بیماران معتاد سالماند یا بیمارانی آه مشکلات قلبی - ریوی دارند چنین ترک شدید و ناگهانی ممکن است به مرگ بیانجامد.

4- ریسک بالای بیمار بهای قلبی و ریوی در مصرف مواد افیونی و سیگار.

# آزمون چالش با نالوکسان ( پروتکل )

ابتدا ۲/. میلی گرم نالوکسان به صورت زیر جلدی تزریق میگردد. در صورت عدم مشاهده علایم ترک ۴/. و سپس ۸/. میلی گرم دیگر به صورت زیر جلدی تزریق می شود. در صورت عدم بروز علایم ترک، درمان با نالترکسون آغاز می شود.(حداقل زمان لازم ۳۰ دقیقه)



# Naloxone challenge test (NCT)

## Intravenous Administration

1. Draw 0.8 mg naloxone into a sterile syringe.
2. Inject 0.2 mg naloxone intravenously.
3. Wait 30 seconds for signs and symptoms of withdrawal. If withdrawal signs/symptoms are present, stop the naloxone challenge and treat symptomatically.
4. If no withdrawal signs and symptoms are present and vital signs are stable, inject remaining naloxone (0.6 mg) and observe for 20 minutes. Check the patient's vital signs and monitor for withdrawal.
5. If withdrawal signs and symptoms are present, stop the naloxone challenge and treat symptomatically. The test can be repeated in 24 hours or the patient can be considered for opioid agonist treatment.
6. If no withdrawal signs and symptoms are present\* and **oral naltrexone is the desired treatment course**, give the patient two tablets of 25 mg naltrexone (take one tablet on each of the next 2 days) and a sufficient number of 50 mg naltrexone tablets (take one 50 mg tablet daily starting on the third day)
7. Instruct the patient about the risk of overdose and death if they use opioids to override the blockade.



# Naloxone challenge test (NCT)

## Subcutaneous Administration

1. Inject 0.8 mg naloxone subcutaneously.
2. Wait 20 minutes while checking vital signs and observing for signs and symptoms of opioid withdrawal.
3. If withdrawal signs and symptom are present, stop the naloxone challenge and treat symptomatically. The test can be repeated in 24 hours or the patient can be considered for opioid agonist treatment.
4. If no withdrawal signs and symptoms are present, follow Step 6 (for oral naltrexone treatment).

# آزمون چالش با نالترکسون خوراکی ( پروتکل )

- 1- ابتدا محتوای یک کپسول ۲۵ میلی گرمی نالترکسون در یک لیوان ۲۵۰ سی سی آب حل می شود. بنابراین هر ۵ سی سی معادل یک قاشق غذاخوری حاوی ۵٪ میلی گرم نالترآسون خواهد بود. در صورت عدم بروز علایم ترک، محتوای لیوان به تدریج در فواصل نیم ساعته در چهار نوبت به صورت خوراکی به بیمار داده می شود.
- 2- برای شروع دو قاشق غذاخوری یعنی یک میلی گرم نالترآسون به بیمار داده شده و مدت نیم ساعت بیمار برای مشاهده علایم ترک تحت نظر گرفته می شود.
- 3- در مرحله بعد ۴ میلی گرم یعنی ۸ قاشق غذاخوری به وی عرضه میشود.
- 4- سپس مابقی محتوای لیوان در دو نوبت ( هر یک ۱۰ میلی گرم) با فاصله نیم ساعت به بیمار داده می شود.
- 5- در صورت تحمل بیمار و عدم بروز علایم ترک، نالترآسون از روز بعد با دوز ۵۰ میلی گرم در روز قابل تجویز است.  
**در صورت مثبت بودن تست باید بعد از بررسی علت ۸۴ ساعت بعد تست تکرار شود**

# تجویز نالترکسون (پروتکل)

تجویز نالترکسون می تواند به دو صورت انجام شود:

1-تجویز روزانه ۵۰ میلی گرم، که برای بسیاری از بیماران حفظ رژیم آن آسان تر است.

2-تجویز سه روز در هفتگی با دوز ۱۰۰ میلی گرم. در این صورت برای اجتناب از فراموش کردن مصرف منظم توسط بیمار، بهتر است روزهایی مصرف به صورت روزهای زوج یا فرد هفتگی از قبل مشخص شوند.**(روز پنجم هفتگه بهتر است ۱۵۰ میلی گرم استفاده کند)**

باید در مورد اهمیت مصرف نالترآسون، به بیمار و خانواده تاکید شود.

می توان توصیه کرد که نالترآسون به صورت محلول در آب پیش روی خانواده مصرف شود تا موجب آسودگی خاطر همه شود.

# دفعات ویزیت و تجدید نسخه (پروتکل)

هفته اول هفته ای یک مرتبه و تا ماه سوم دو هفته یک مرتبه.

اگر بیمار بیکار است، بهتر است پس از ماه سوم نیز هر دو هفته یک بار ویزیت شود.

اگر سر کار میرود ویزیت ماهی یک بار.

لازم است در هر نوبت مراجعه، بیمار نالتراسون آن روز را به صورت محلول در آب در حضور پرسنل درمانی بیاشامد.

برای اجتناب از بروز علایم ترک، پرسنل درمانی باید پیش از ارایه نالتراسون به بیمار یک بار دیگر از وی در مورد لغزش احتمالی و مصرف مواد افیونی سئوال و در مورد بروز علایم شدید ترک در صورت مصرف نالتراسون پس از مصرف این مواد به بیمار هشدار دهند.

# بروز علایم ترک حین درمان ( پروتکل )

- 1- معمولاً بیماران به خوبی با عوارض شدید ترک ناشی از مصرف نالترکسون به دنبال مصرف جانبی مواد مطلع هستند. در هر صورت باید در مورد چنین مشکلی پیش از ارایه نالترکسون به آنها هشدار داده شود.
- 2- گاهی برخی از بیماران بی تجربه این هشدار را جدی نگرفته و به نوشیدن نالترکسون در حضور پرسنل علیرغم مصرف مواد افیونی مبادرت میورزند.
- درمان : مانند سایر علایم ترک با استفاده از کلونیدین، بنزوپنیدین، داروهای مسکن صورت میگیرد. ممکن است در مواردی لازم باشد بیمار حداقل برای چند ساعت تحت نظر گرفته شود.
- 3- در موارد خاص، بخصوص در صورت وجود مشکلات قلبی عروقی، بسترهای کوتاه مدت الزامی است.
- 4- در موارد نادر به علت علایم شدید میتوان از بوپرنورفین کمک گرفت. اما باید در نظر داشت که تمایل گیرنده های افیونی برای نالترآسون شدید و استفاده از داروهایی با تمایل کمتر نظیر مورفین معمولاً کمک چندانی به بهبود علایم ترک نخواهند کرد.



# Clinical use

- ▶ Because of its long duration of action, naltrexone has been proposed as a maintenance drug for addicts in treatment programs.
- ▶ There is evidence that naltrexone decreases the craving for alcohol in chronic alcoholics by increasing baseline  $\beta$ -endorphin release, and it has been approved by the FDA for this purpose.
- ▶ Naltrexone also facilitates abstinence from nicotine (cigarette smoking) with reduced weight gain.
- ▶ Combination of naltrexone plus bupropion may also offer an effective and synergistic strategy for weight loss.

# Side effect

## More common

- Abdominal or stomach cramping or pain (mild or moderate)
- anxiety, nervousness, restlessness or trouble sleeping
- headache
- joint or muscle pain
- nausea or vomiting
- unusual tiredness

## Less common

- Chills
- constipation
- cough, hoarseness, runny or stuffy nose, sinus problems, sneezing, or sore throat
- diarrhea
- dizziness
- fast or pounding heartbeat
- increased thirst
- irritability
- loss of appetite
- sexual problems in males

# Healthcare Professionals

## Nervous system

- ▶ **Very common** (10% or more): Headache (25%), dizziness/syncope (13%)
- ▶ **Common** (1% to 10%): Somnolence/sedation
- ▶ **Frequency not reported:** Lethargy, cerebral arterial aneurysm, convulsions, disturbance in attention, dysgeusia, mental impairment, migraine, ischemic stroke, paresthesia

# Healthcare Professionals

## Psychiatric

- ▶ **Very common** (10% or more): Insomnia/sleep disorder (14%), anxiety (12%)
- ▶ **Common** (1% to 10%): Depression
- ▶ **Uncommon** (0.1% to 1%): Suicide attempt/ideation
- ▶ **Frequency not reported**: Irritability, abnormal dreams, agitation, alcohol withdrawal syndrome, euphoric mood, delirium, libido decreased

# Healthcare Professionals

## Gastrointestinal

- ▶ **Very common** (10% or more): Nausea (33%), vomiting NOS (14%), diarrhea (13%), abdominal pain (11%)
- ▶ **Common** (1% to 10%): Dry mouth, toothache
- ▶ **Frequency not reported:** Abdominal discomfort, colitis, constipation, flatulence, gastroesophageal reflux disease, gastrointestinal hemorrhage, hemorrhoids, pancreatitis acute, paralytic ileus



# Healthcare Professionals

## Hepatic

- ▶ **Very common** (10% or more): Alanine aminotransferase increased (13%), aspartate aminotransferase increased (10%)
- ▶ **Common** (1% to 10%): Gamma-glutamyltransferase increased
- ▶ **Frequency not reported:** Lymphadenopathy including cervical adenitis, white blood cell count increased, cholecystitis acute, cholelithiasis

# Healthcare Professionals

## Musculoskeletal

- ▶ **Very common** (10% or more): Arthralgia/arthritis/joint stiffness (12%)
- ▶ **Common** (1% to 10%): Back pain/stiffness, muscle cramps
- ▶ **Frequency not reported**: Chills, joint stiffness, muscle spasms, myalgia, pain in limb

# Healthcare Professionals

## Cardiovascular

- ▶ **Frequency not reported:** Angina pectoris, angina unstable, atrial fibrillation, cardiac failure congestive, coronary artery atherosclerosis, myocardial infarction, palpitations, deep vein thrombosis[\[Ref\]](#)

## Respiratory

- ▶ **Frequency not reported:** Chronic obstructive pulmonary disease, dyspnea, pharyngolaryngeal pain, sinus congestion[\[Ref\]](#)

## Dermatologic

- ▶ **Common** (1% to 10%): Rash

# Healthcare Professionals

## Metabolic

- ▶ **Very common** (10% or more): Anorexia/appetite decreased NOS/appetite disorder NOS (14%)
- ▶ **Frequency not reported:** Weight decreased, weight increased, appetite increased, dehydration

## Renal

- ▶ **Very common** (10% or more): Abnormal creatinine phosphokinase levels (17%)<sup>[Ref]</sup>

## Immunologic

- ▶ **Very common** (10% or more): Pharyngitis



# Liver disease

- ▶ Skin and eyes that appear yellowish (jaundice)
- ▶ Abdominal pain and swelling
- ▶ Swelling in the legs and ankles
- ▶ Itchy skin
- ▶ Dark urine color
- ▶ Pale stool color
- ▶ Chronic fatigue
- ▶ Nausea or vomiting
- ▶ Loss of appetite
- ▶ Tendency to bruise easily



# Risk of opioid overdose.

Accidental overdose can happen in two ways.

1. Naltrexone blocks the effects of opioids, such as heroin or opioid pain medicines. Patients who try to overcome this blocking effect by taking large amounts of opioids may experience serious injury, coma, or death.
2. After receiving a dose of naltrexone, the blocking effect slowly decreases and completely goes away over time. Patients who are taking naltrexone for an OUD can become more sensitive to the effects of opioids at the dose used before, or even lower amounts. Using opioids while on naltrexone can lead to overdose and death.



# Metabolism

- ▶ Both formulations are extensively metabolized by the kidneys and liver, but without CYP450 enzyme system involvement.
- ▶ Limited potential drug–drug interactions.
- ▶ Major metabolite, 6-beta naltrexol, is also a mu-opioid receptor antagonist. It is eliminated primarily by the kidneys in the urine.
- ▶ **Orally administered naltrexone has a half-life of approximately 4 hours.** Its primary metabolite, 6-beta-naltrexol, is a weak mu-opioid receptor antagonist with a half-life of approximately 12 hours.



# Drug addiction and Epigenetic



# What is Addiction? AS a Disease

“Chronically relapsing disorder that is characterized by 3 major elements:

- I) Compulsion to seek and take the drug
- II) Loss of control in limiting intake
- III) Emergence of a negative emotional state when access to drug is prevented”

# Kinds of Addiction?

- • Heroin addiction
- • Cocaine addiction
- • Alcohol addiction (“alcoholism”)
- • Marijuana addiction
- • Amphetamines addiction
- • Nicotine addiction

# Other Kinds of addiction?

- Sex addiction??
- Gambling addiction??
- Food addiction??
- Shopping addiction????
- Internet addiction????
- Cell phone addiction????

# **Drug Abuse and Addiction are Among the Most Serious Public Health Problems Facing Our Society**

- and Frequently Coexist  
with Other Mental and  
Physical Disorders

# Factors initiated Drug Abuse

- Reward & Pleasure
- Diseases (Pain, Depression, Anxiety &....)
- Genetic

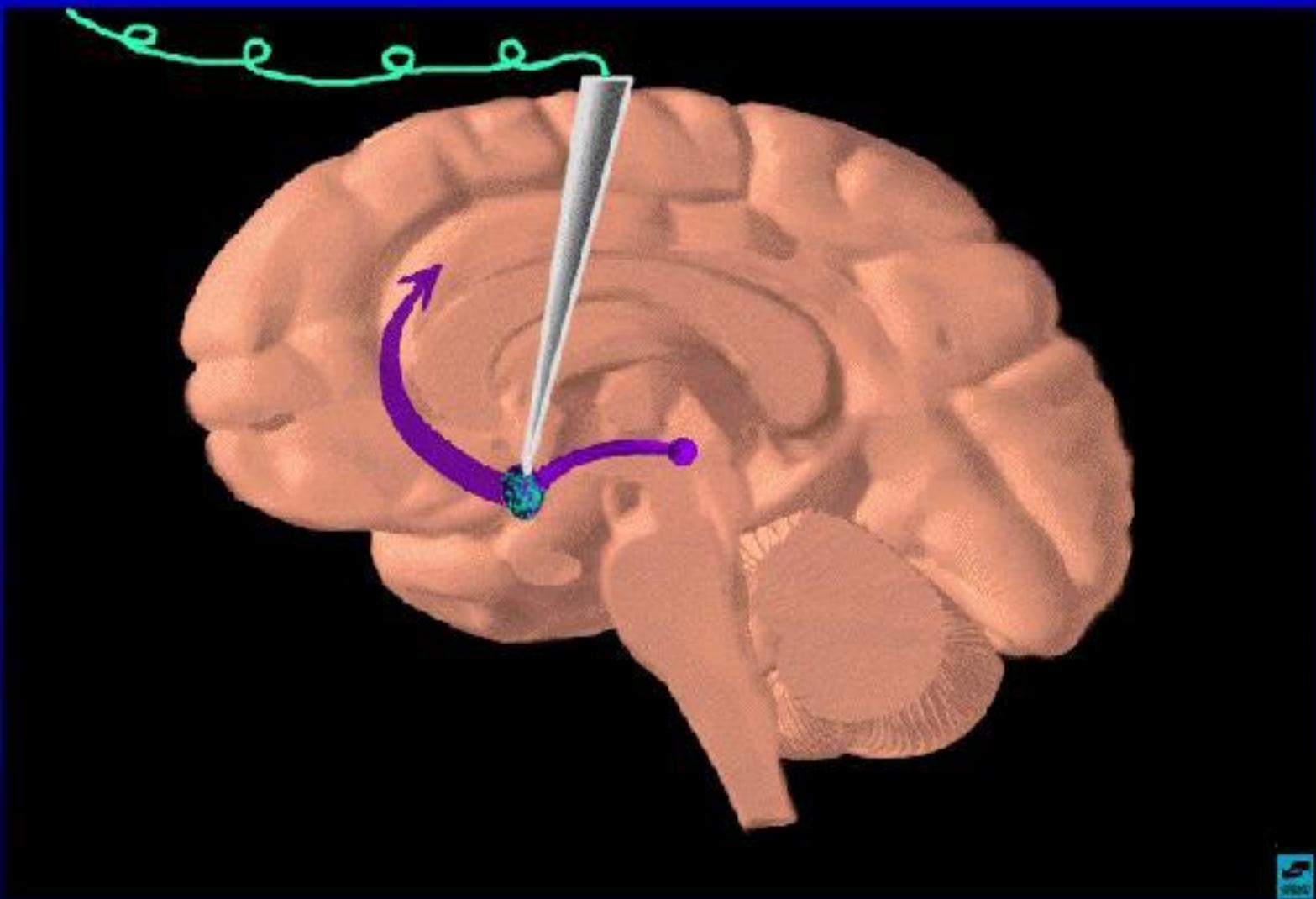


# REWARD

# **History**

- James Olds (1954)
- Pleasure is a distinct neurobiological function that is linked to a complex reward & reinforcement system
- Biochemical & Biological studies

# James Olds (1954)



# **Drug Reward**

- **Reward:** A response to a stimulus which causes pleasure; natural reward (food, liquids, sex) as well as electrical stimulation and many drugs
- **Reinforcement:** Continuing an action which has been shown reward previously

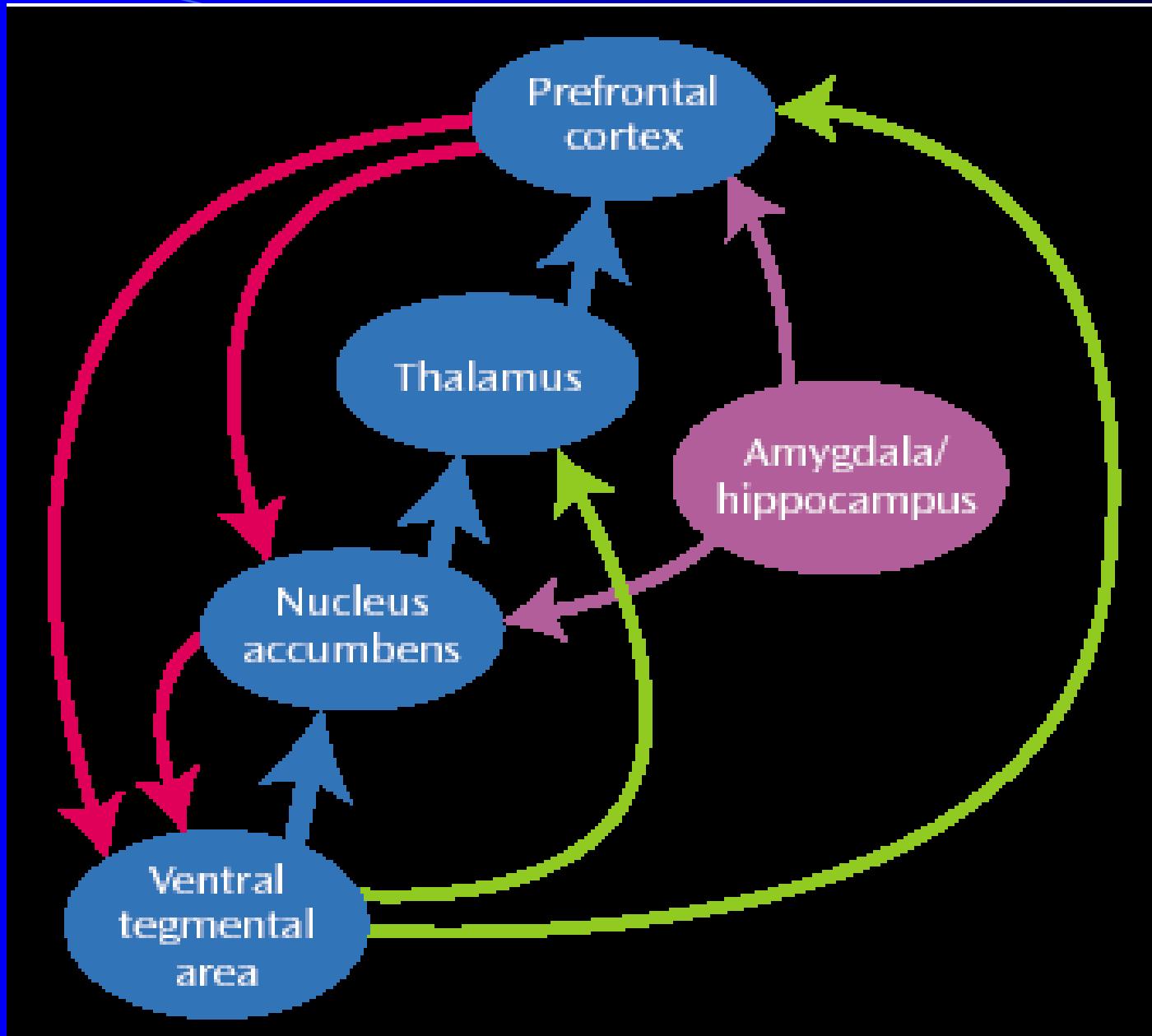
# **Systems involves in biology of**

## **REWARD**

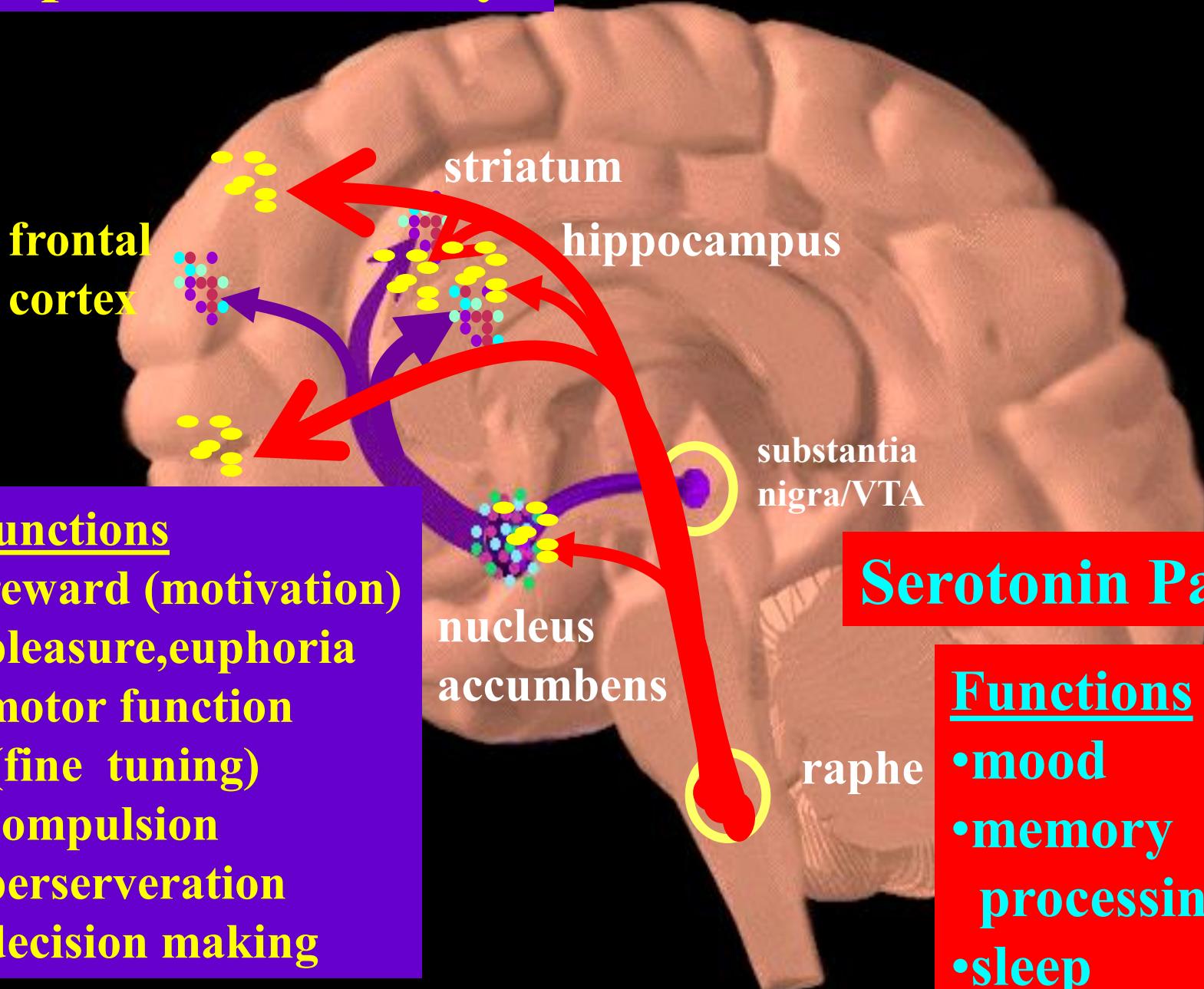
- Serotonin in Hypothalamus
- Enkephalins (opioid peptide) in VTA & Nucleus accumbens
- GABA in VTA & Nucleus accumbens
- NE (Release of NE in Hyppocampus from neuronal fibers that originate in the LC)

# **Importance of Reward**

- Reinforcement (Reward) leads to more drug administration
- Which may lead to drug tolerance
- To gain the previous drug effect after tolerance induction, Higher doses of drug is needed which may cause dependence



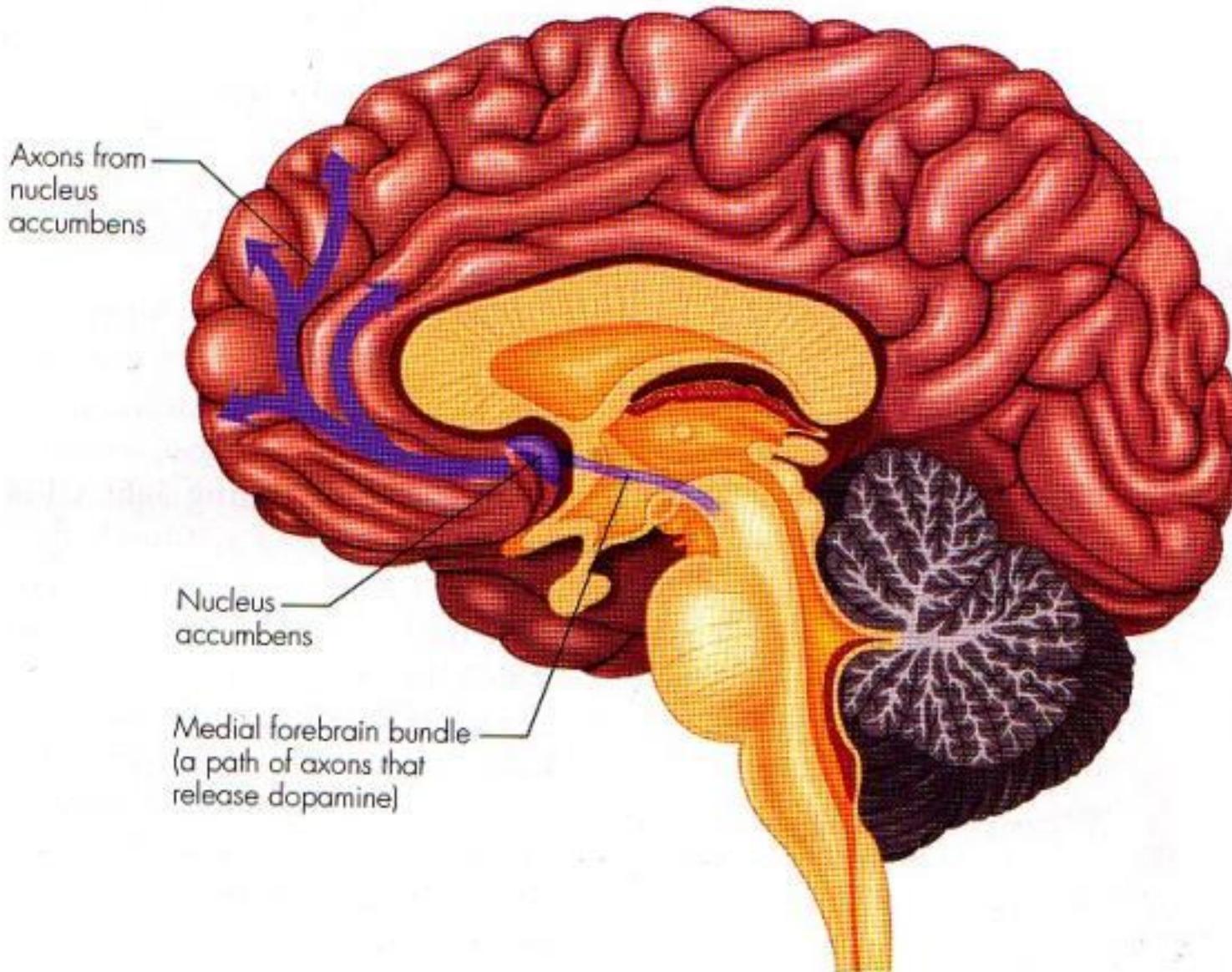
# Dopamine Pathways

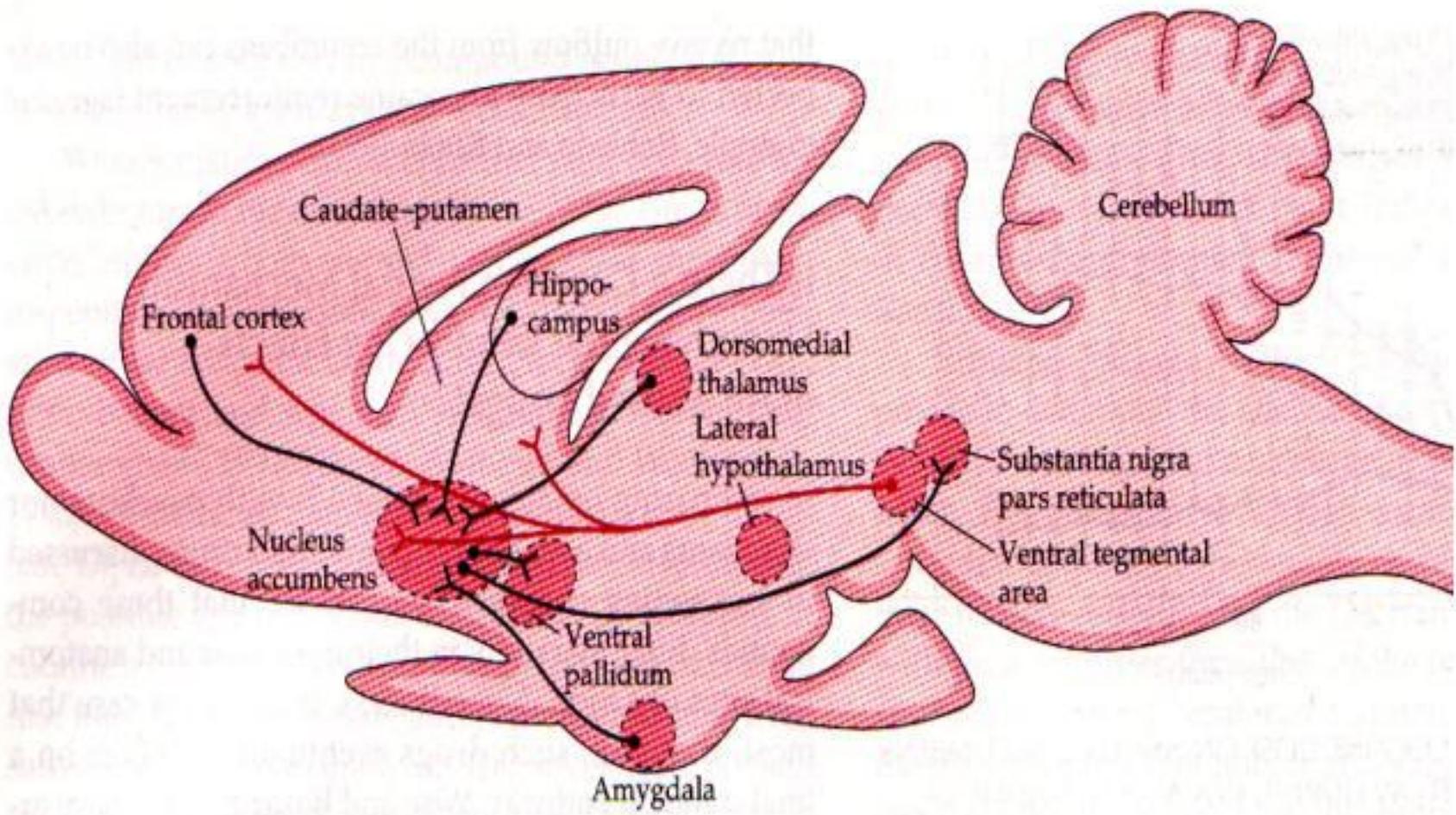


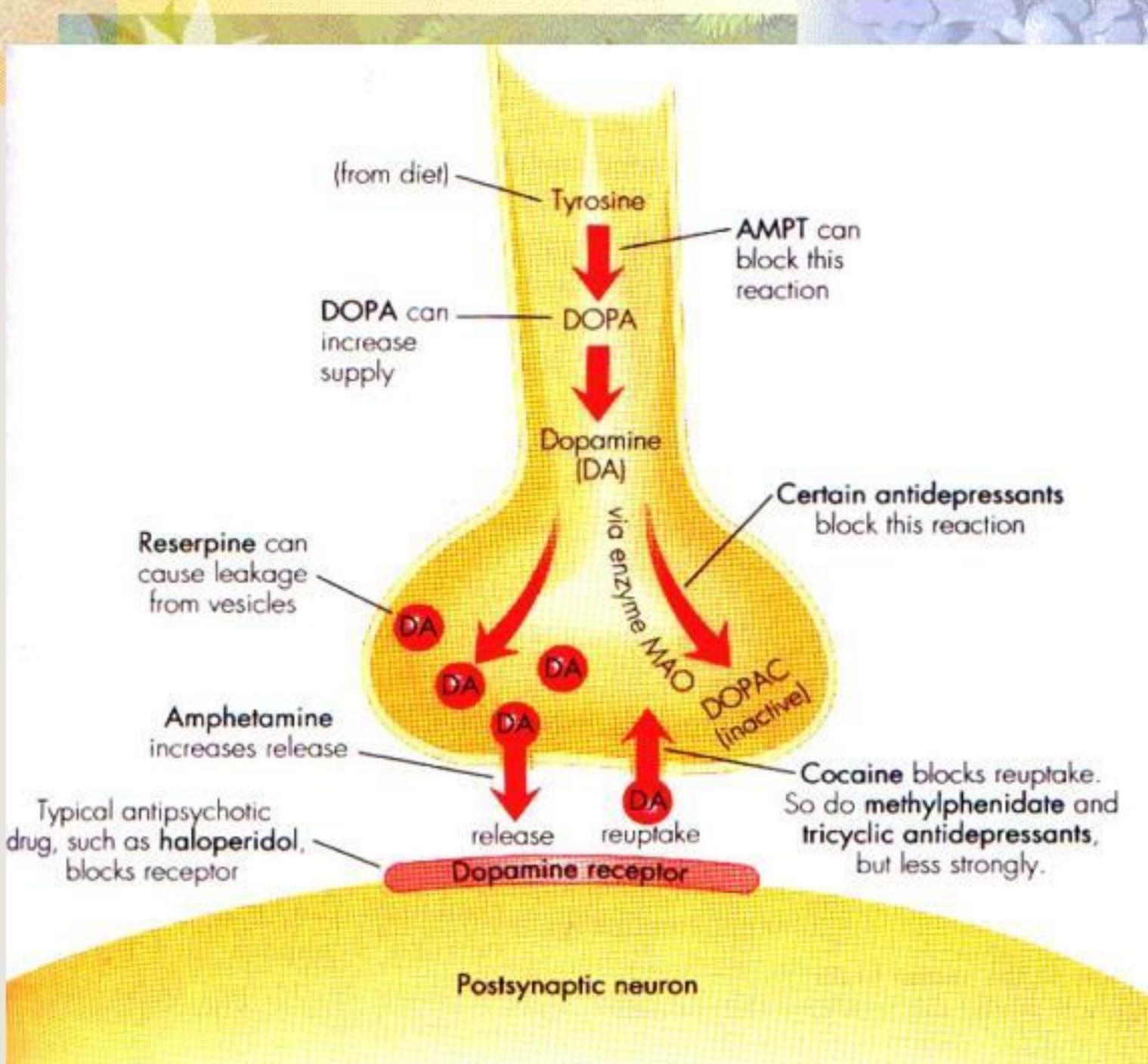
# Dopaminergic System

Is

the final common pathway







# Dopamine receptors

- D<sub>1</sub> type (D<sub>1</sub> & D<sub>5</sub>) increase cAMP
- D<sub>2</sub> type (D<sub>2</sub>, D<sub>3</sub> & D<sub>4</sub>) decrease cAMP

# Reward Pathway

The following neurotransmitters act on the reward pathway:

<b>Dopamine</b> <ul style="list-style-type: none"><li>• Receptors: D1, D2</li><li>• Function: pleasure, euphoria, mood, motor function</li></ul>	<b>Serotonin</b> <ul style="list-style-type: none"><li>• Receptors: 5HT3</li><li>• Function: mood, impulsivity, anxiety, sleep, cognition</li></ul>
<b>Cannabinoids</b> <ul style="list-style-type: none"><li>• Receptors: CB1, CB2</li><li>• Function: Pain, appetite, memory</li></ul>	<b>Opioid peptides (Endorphins, Enkephalins)</b> <ul style="list-style-type: none"><li>• Receptors: Kappa, Mu, Delta</li><li>• Function: pain</li></ul>

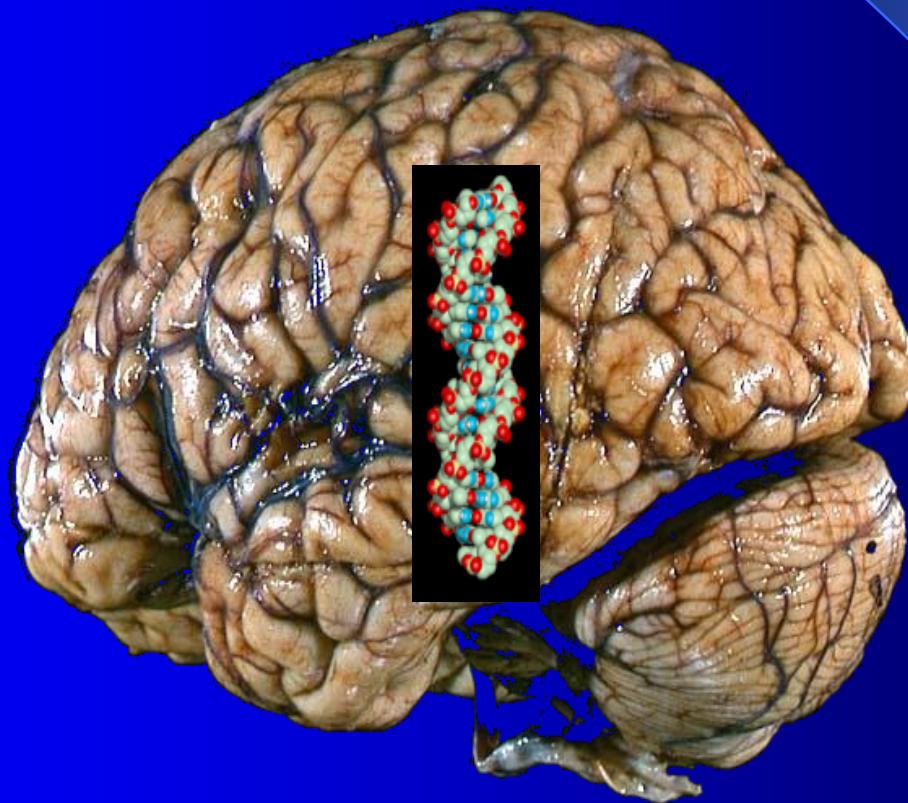
In all rewards, dopamine is the final activation chemical

# Reward Pathway

Neurotransmitters and anatomical sites involved in the acute reinforcing effects of drugs of abuse

<b>Dopamine</b>  Ventral tegmental area, nucleus accumbens	<b>Opioid Peptides</b>  Nucleus accumbens, amygdala, ventral tegmental area
<b>GABA</b>  Amygdala, bed nucleus of stria terminalis	<b>Glutamate</b>  Nucleus accumbens

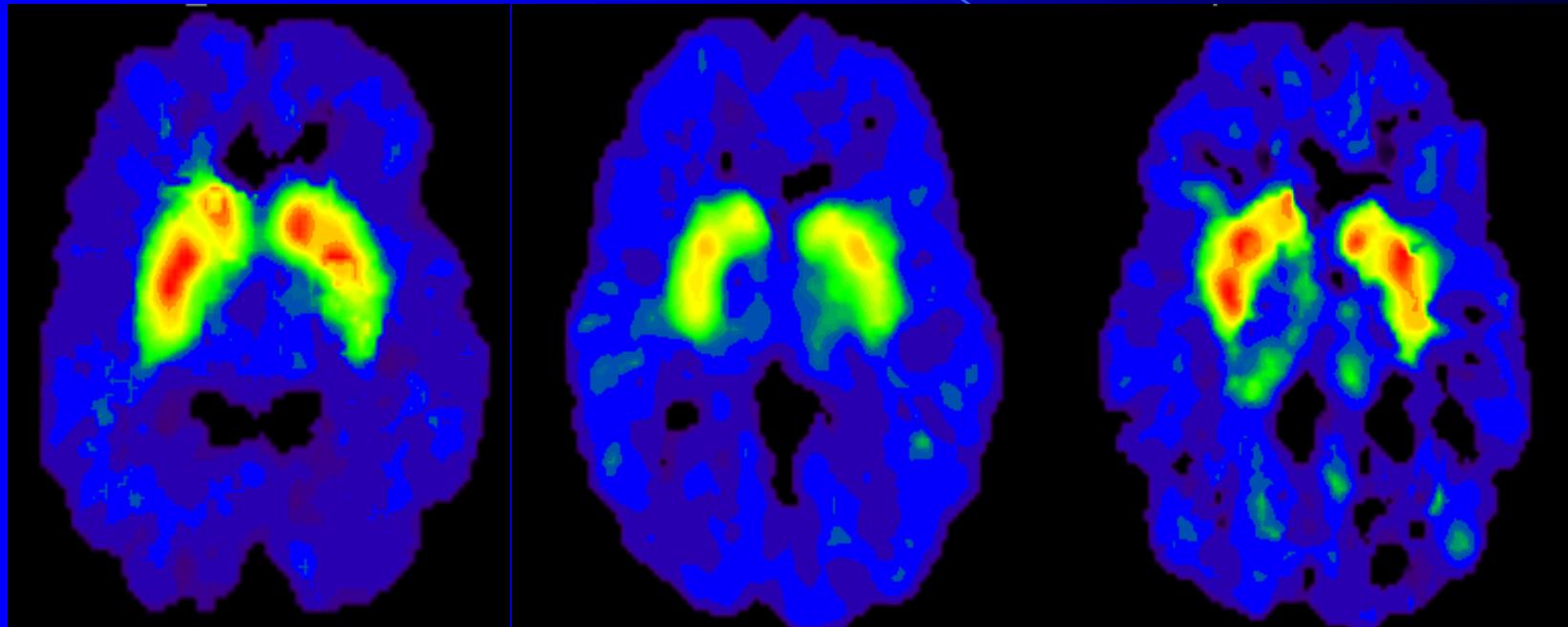
# Drug addiction and Epigenetic



# **Common Underlying Neurobiological Factors Can Be:**

- **Neurochemical** (imbalance of neurotransmitters)
- **Structural/anatomical** (same regions and pathways)
- **Genetic** (inherited factors that compromise function)

# Why is Continued Treatment Critical?



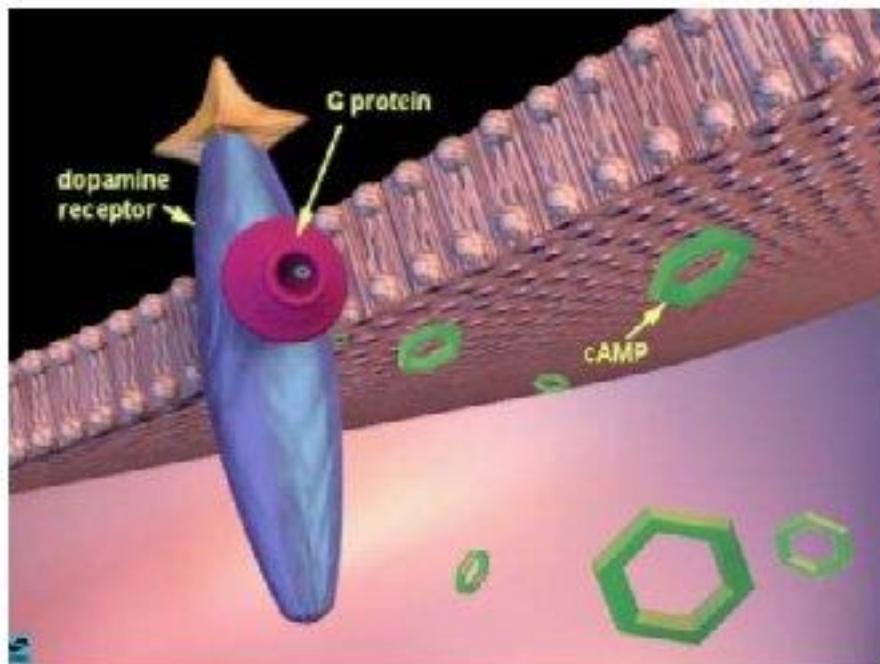
Normal Control

Meth user  
(1 month abstinent)

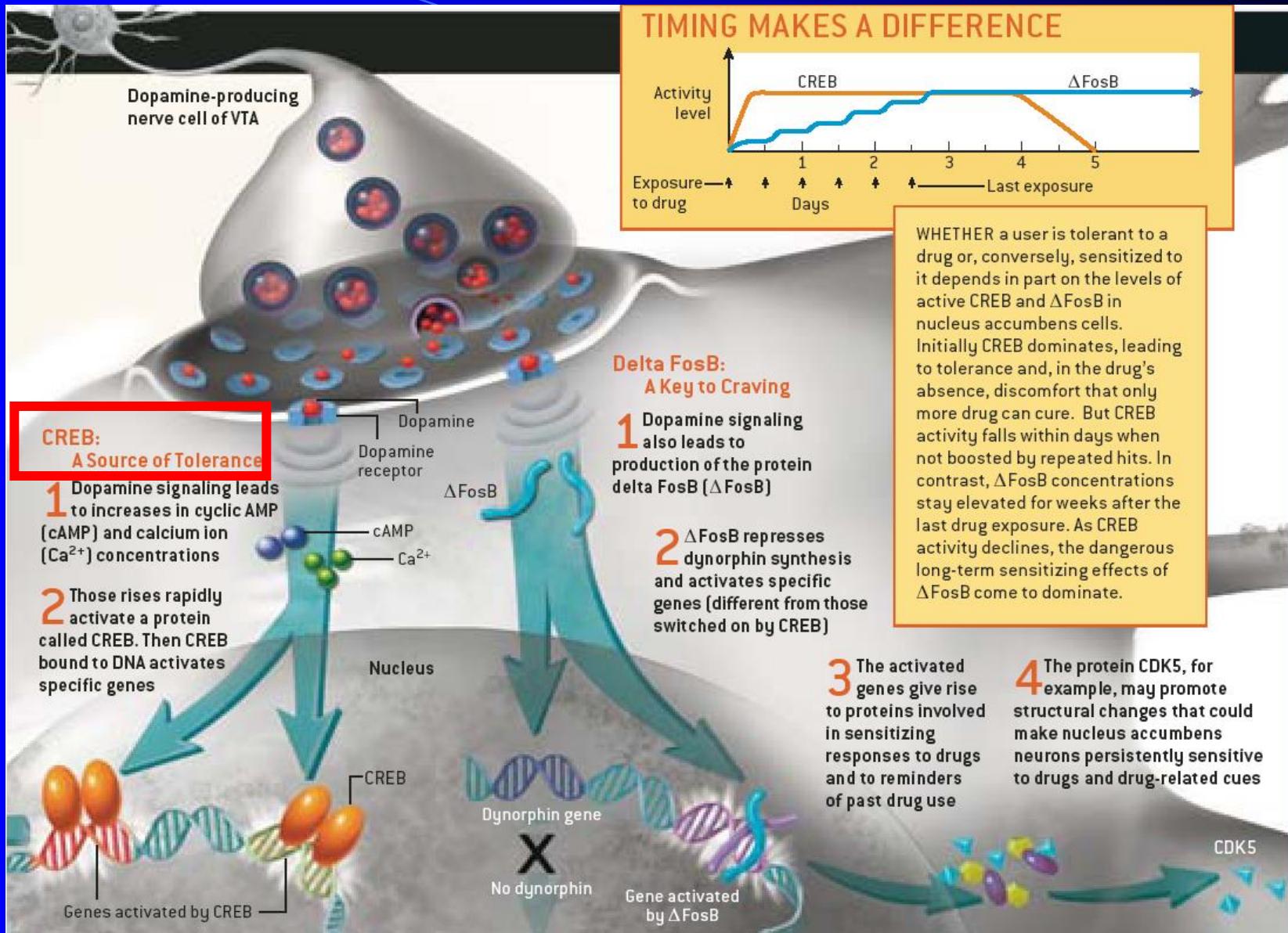
Meth user  
(36 months abstinent)

**Partial Recovery of Dopamine Transporters  
After Prolonged Abstinence**

# Dopamine & cAMP



- activation of dopamine receptors causes
  - increased production of cAMP inside the post-synaptic cell.
  - many changes inside neuronal cells lead to **abnormal firing patterns**
  - there are **increased impulses** leaving the **nucleus accumbens** to activate the **reward system**



# Common Molecular Changes Associated with Dependence

- **Dopamine D-2 receptor binding**

decreased in human imaging studies in dependent subjects

- **CREB ( cyclic adenosine monophosphate response element binding protein) transcription factor**

decreased in nucleus accumbens and extended amygdala during the development of dependence

- **Delta-FosB transcription factor**

changed during protracted abstinence to drugs of abuse

## Definition

**Drug Addiction** can be viewed as a stable form of drug-induced neural plasticity, whereby long-lasting changes in gene expression mediate some of the stable behavioral abnormalities that define an addicted state.

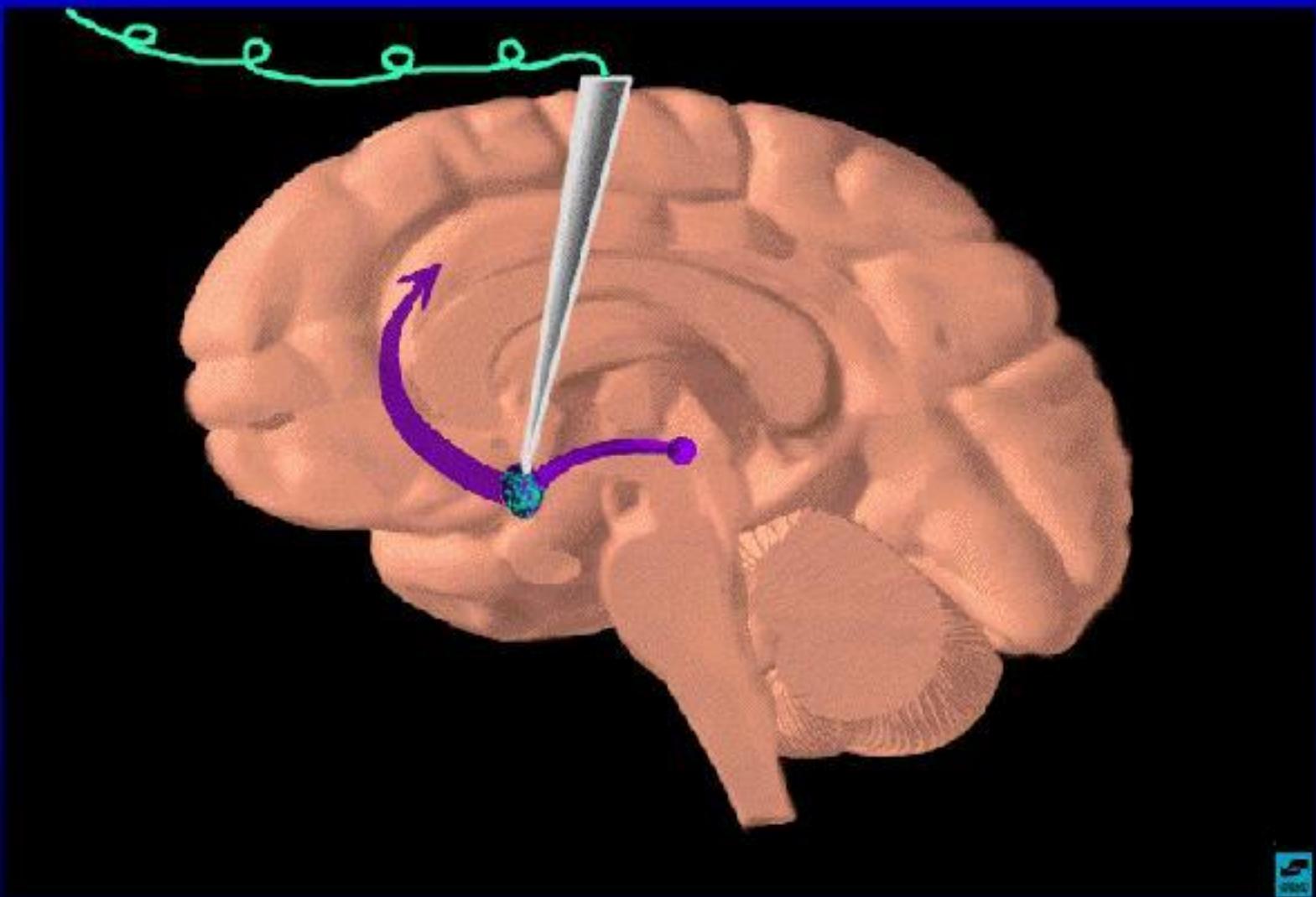
**Epigenetic** is interactions between genes and the environment that result in specific biological phenotypes.

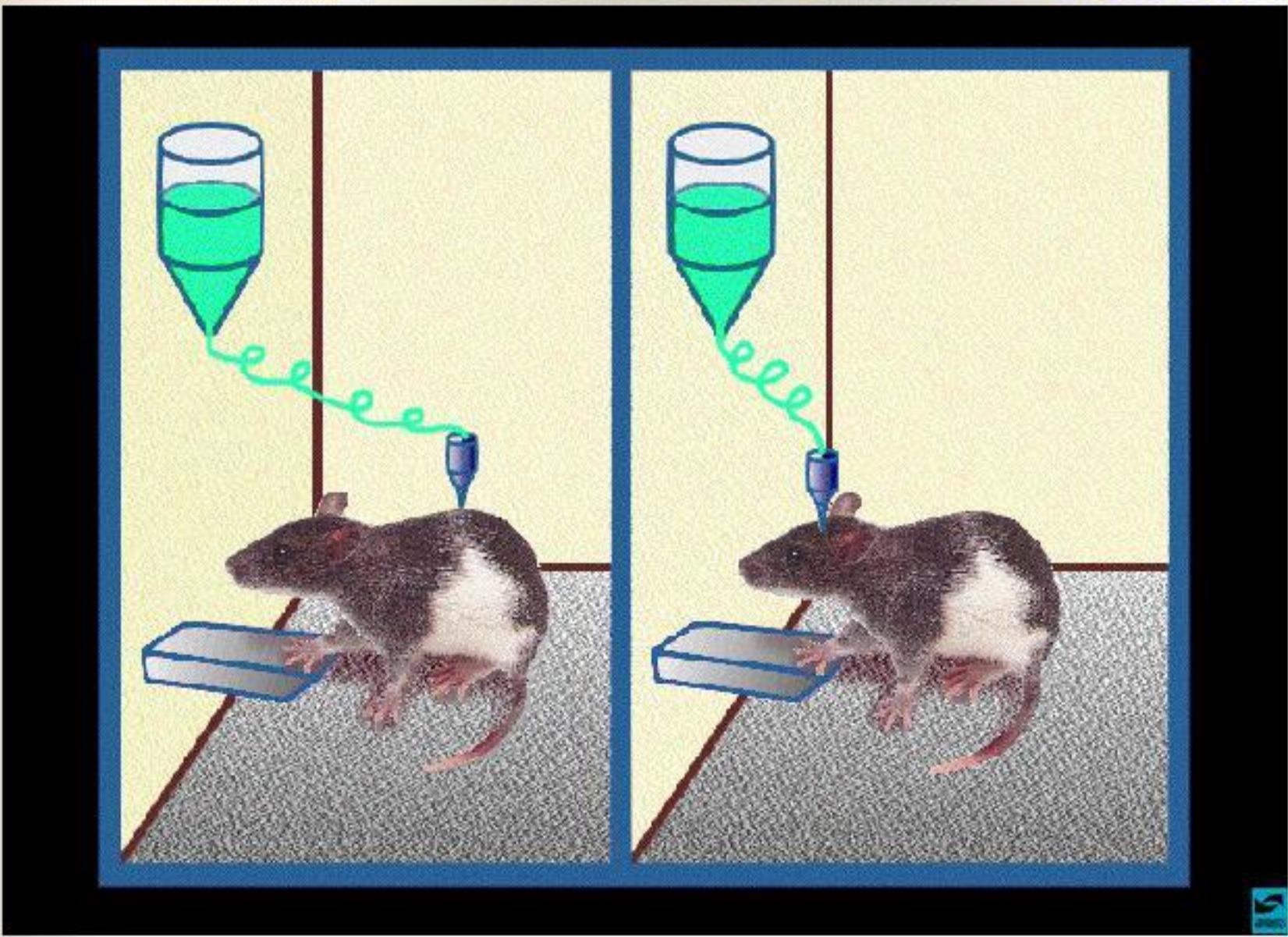
# **Animal Models**

## **(Based on Conditioning)**

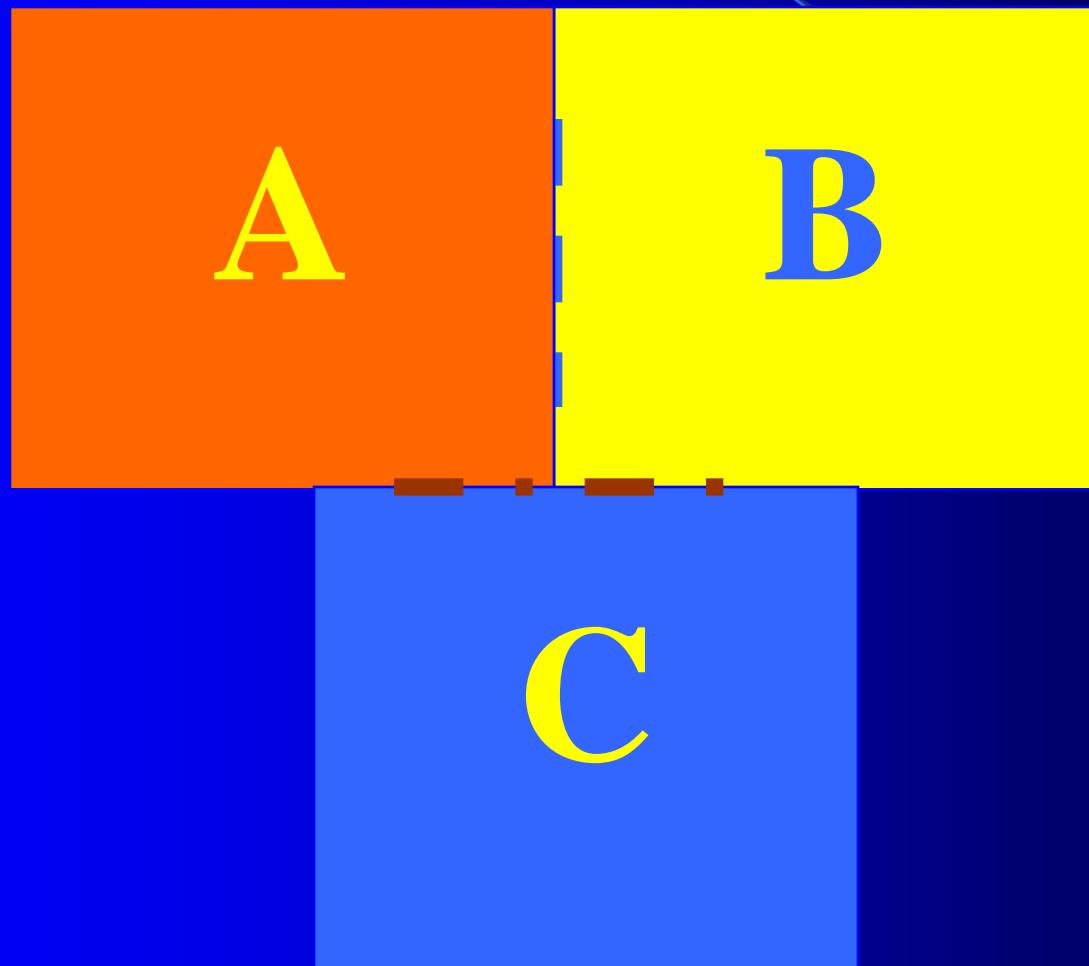
- Intracranial Self-stimulation
- Drug Self-administration
- Conditioning Place Preference

# James Olds (1954)



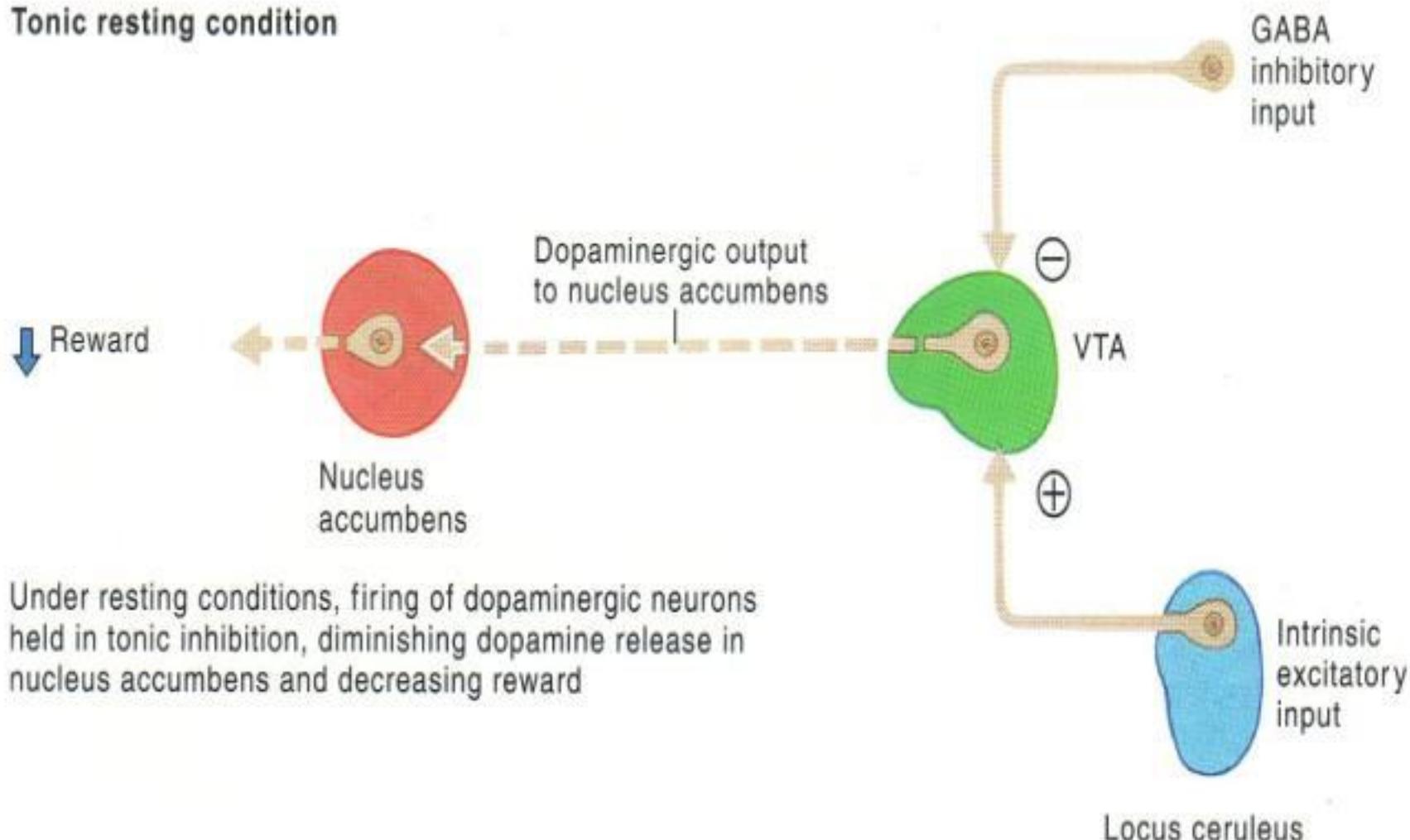


# CPP Apparatus

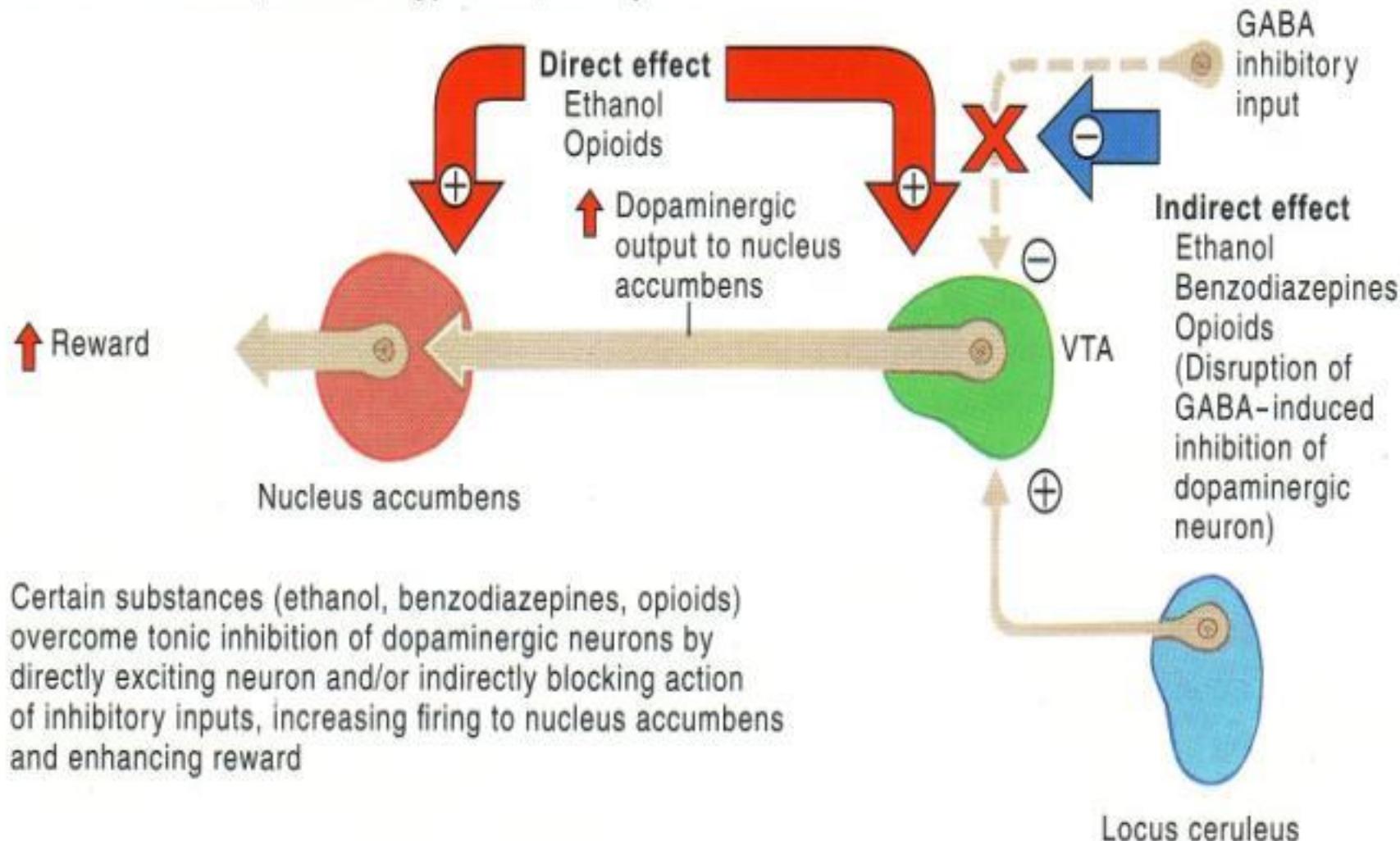


## Drug Action Mechanisms in Brain Reward Circuit

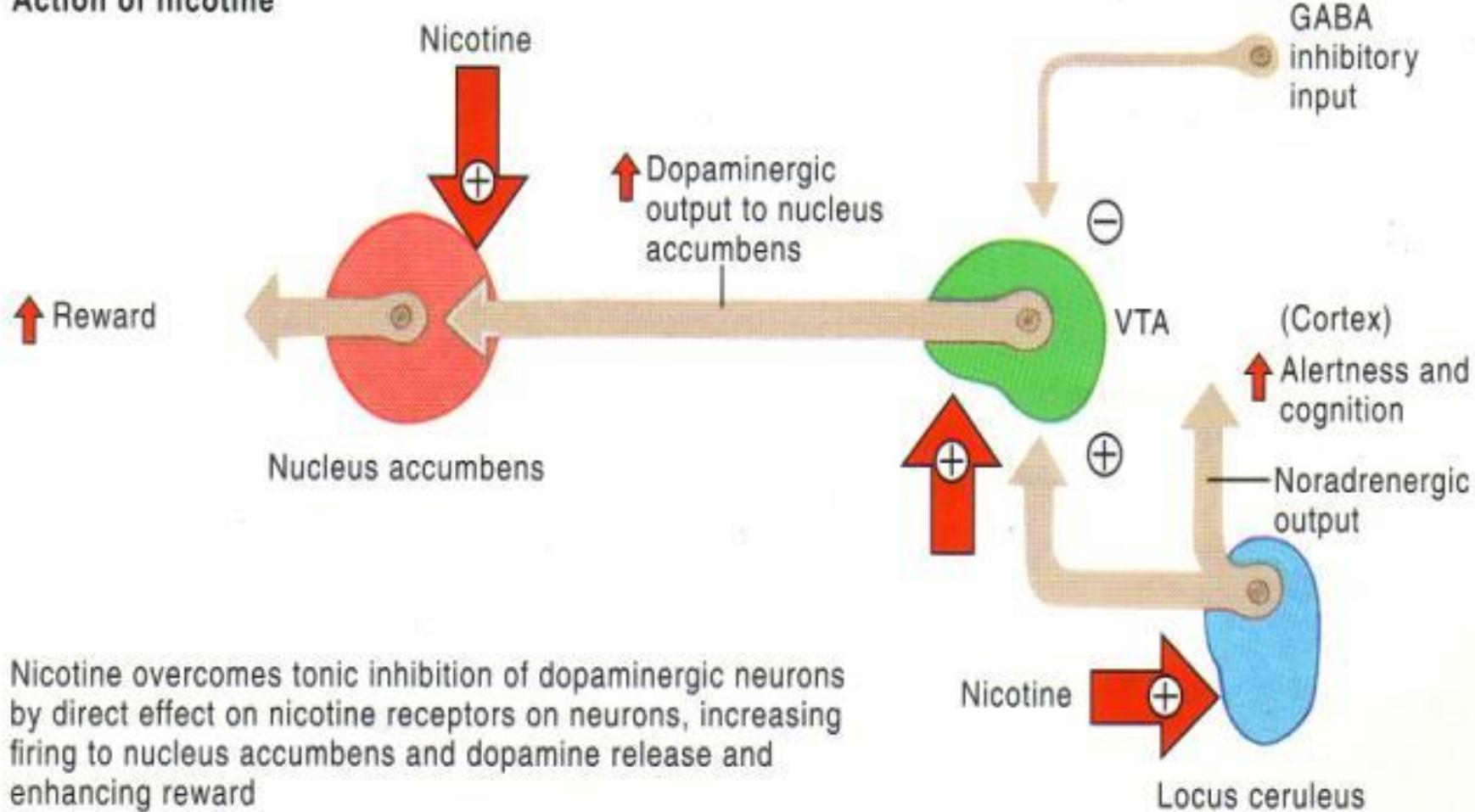
Tonic resting condition



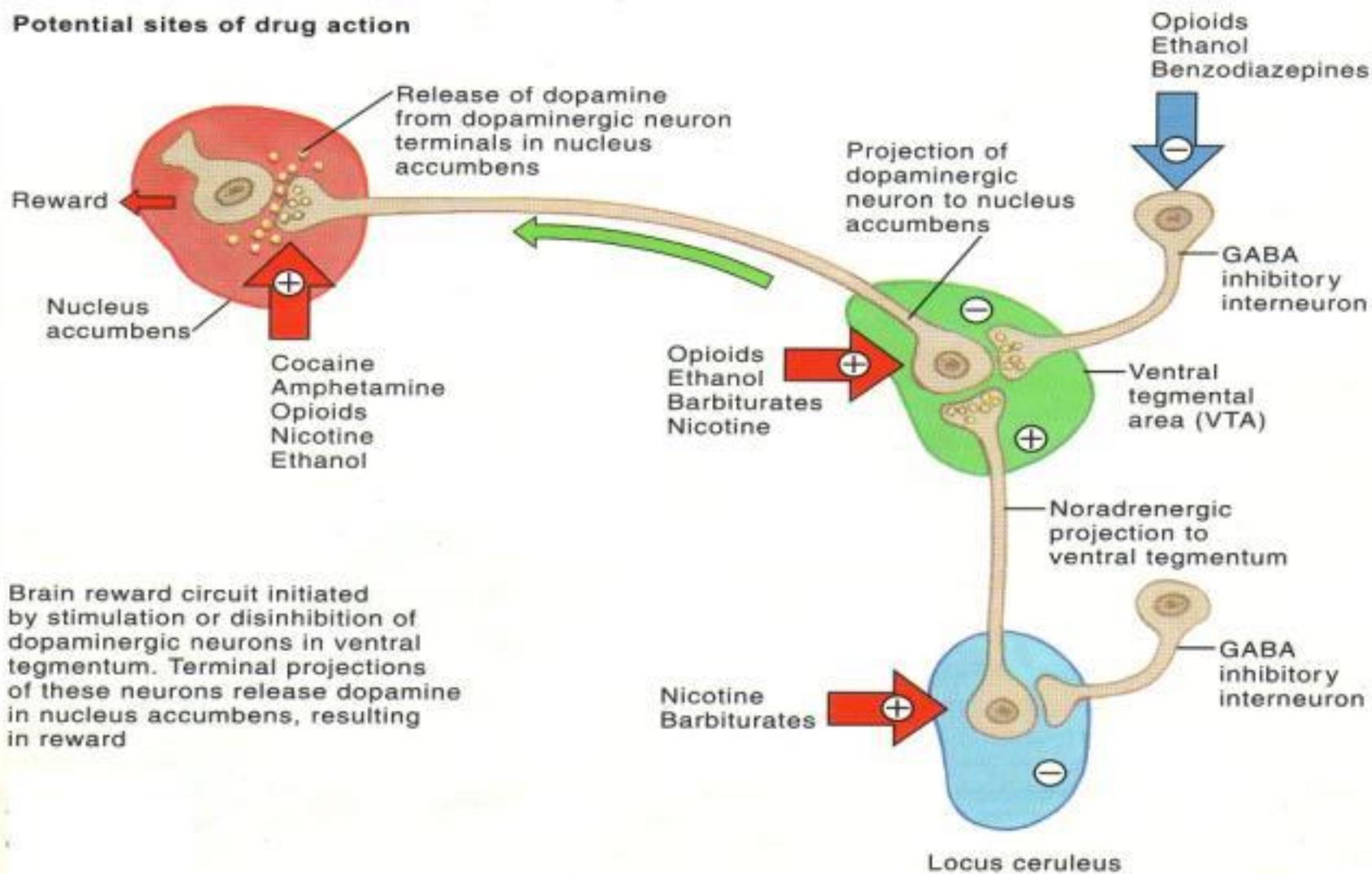
## Action of alcohol, sedative/hypnotics, and opioids



## Action of nicotine



## Potential sites of drug action





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Ph.D. in Epidemiology  
Iranian National Center for Addiction studies  
Tehran University of Medical Sciences



TEHRAN UNIVERSITY  
OF  
MEDICAL SCIENCES

# Studies on Addiction

Methodology in addiction studies is critical for understanding the complex interplay of biological, psychological, and social factors that contribute to substance use disorders. Researchers often employ a combination of quantitative and qualitative approaches to capture a comprehensive view of addiction.



Quantitative methods may include randomized controlled trials, longitudinal studies, and surveys that assess patterns of substance use, treatment outcomes, and relapse rates.



Qualitative methods, such as interviews and focus groups, provide deeper insights into individuals' experiences, motivations, and barriers to recovery. Additionally, the use of mixed-methods approaches allows for triangulation of data, enhancing the validity of findings. Ethical considerations are paramount, particularly regarding informed consent and the confidentiality of vulnerable populations.

Overall, robust methodology in addiction studies not only advances scientific understanding but also informs effective interventions and policies aimed at reducing the impact of addiction on individuals and communities.



# Challenges in Addiction studies

Addiction studies face significant challenges, beginning with the **definition of addiction itself**.

The term can encompass a wide range of behaviors and substances, making it difficult to create a universally accepted definition.

Variability in the conceptualization of addiction—whether as a **medical condition**, a **behavioral issue**, or a combination of both—complicates research efforts and can lead to inconsistencies in findings.

# Challenges in Addiction studies

Another major difficulty in addiction studies lies in accessing **hidden populations**, such as those who may not seek treatment due to the **stigma** associated with addiction. This taboo can result in **underreporting** and **underestimation** of addiction prevalence, as individuals may be reluctant to disclose their substance use or related behaviors. This reluctance is compounded by **societal judgments** and misconceptions about addiction, which can deter individuals from participating in studies or seeking help.

# Challenges in Addiction studies

Consequently, researchers may struggle to obtain **representative samples**, leading to skewed data that fails to accurately reflect the true scope of addiction in various communities. Additionally, interviewing individuals about their addiction experiences can be **sensitive**; the fear of judgment or legal repercussions may inhibit open and honest communication, further complicating the research process.

# Indicators: prevalence and incidence rates

Understanding the landscape of addiction requires a comprehensive examination of several key indicators. The extent of drug use and abuse is often measured through prevalence and incidence rates, which help researchers determine how widespread drug use is within a population and identify emerging trends.

# Indicators: Characteristics of people using drugs

Additionally, assessing risk and protective factors is crucial, as these elements—such as **socio-economic status**, **mental health**, and **social support**—can significantly influence an individual's likelihood of engaging in drug use.

Drug use patterns, including the **frequency** and **context of use**, provide insights into how substances are consumed, which can inform prevention and intervention strategies. Moreover, **characteristics** of people using drugs, such as age, gender, and ethnicity, help tailor approaches to specific demographics, ensuring more effective outreach and treatment.

# Indicators: Drug abuse-related harms and Risk behaviors

Equally important are the indicators related to the **consequences** of drug use. **Risk behaviors** associated with drug use, such as unprotected sex or driving under the influence, highlight the potential for **negative outcomes** not only for individuals but also for their communities. **Drug abuse-related harms**, including health complications and social repercussions, underscore the need for effective public health responses.

# Indicators: Policy and laws

Policy-related indicators assess the effectiveness of laws and regulations surrounding drug use, while intervention-related indicators evaluate the success of treatment and prevention programs. Finally, supply-related indicators help monitor the availability of drugs within a community, which can impact usage rates and inform strategies for reducing access to harmful substances. Together, these indicators create a multidimensional framework for understanding addiction and guiding effective responses.



The evidence is clear:  
**Invest in Prevention**

**International Day against  
Drug Abuse and Illicit Trafficking**

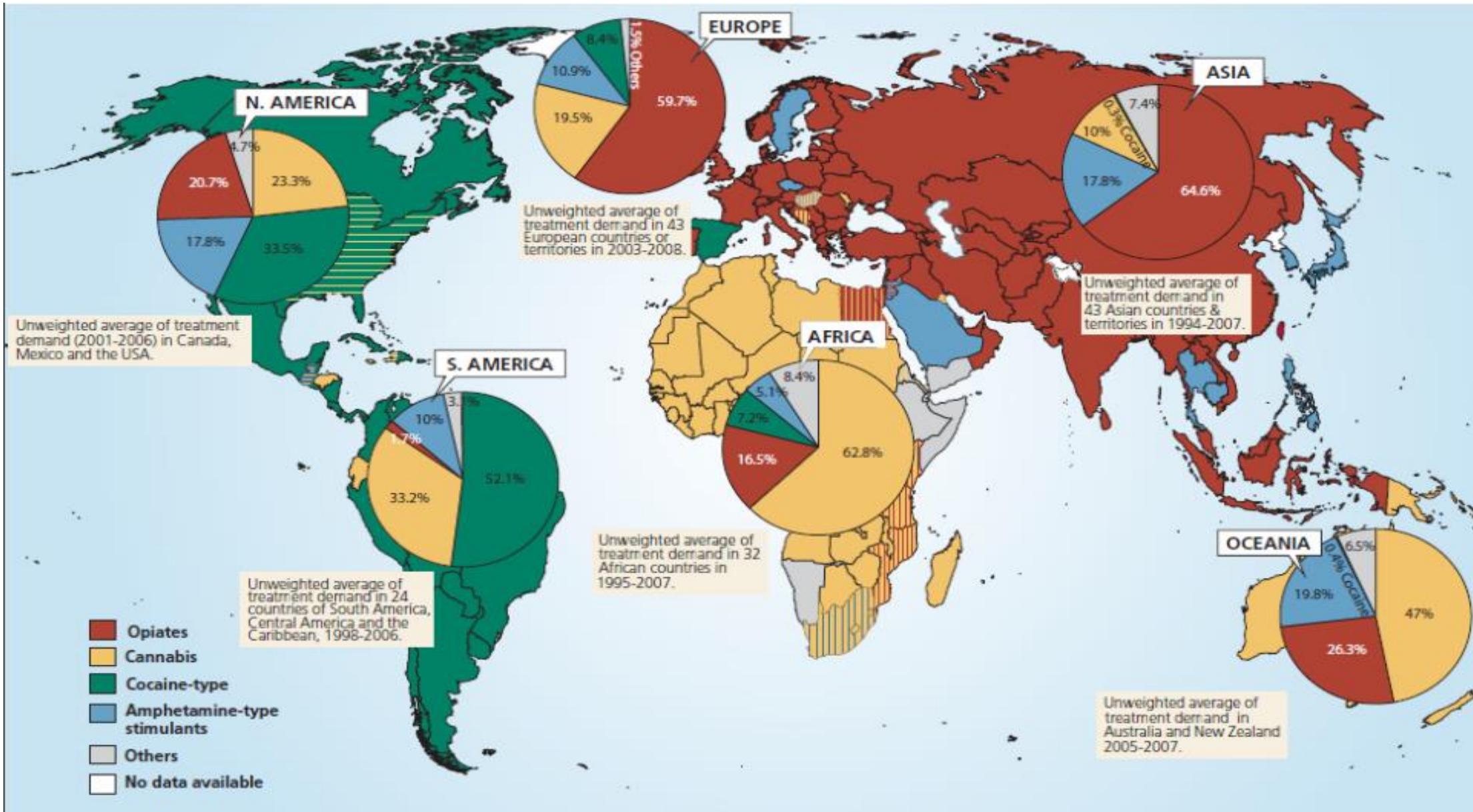
# WORLD DRUG DAY | 26 June

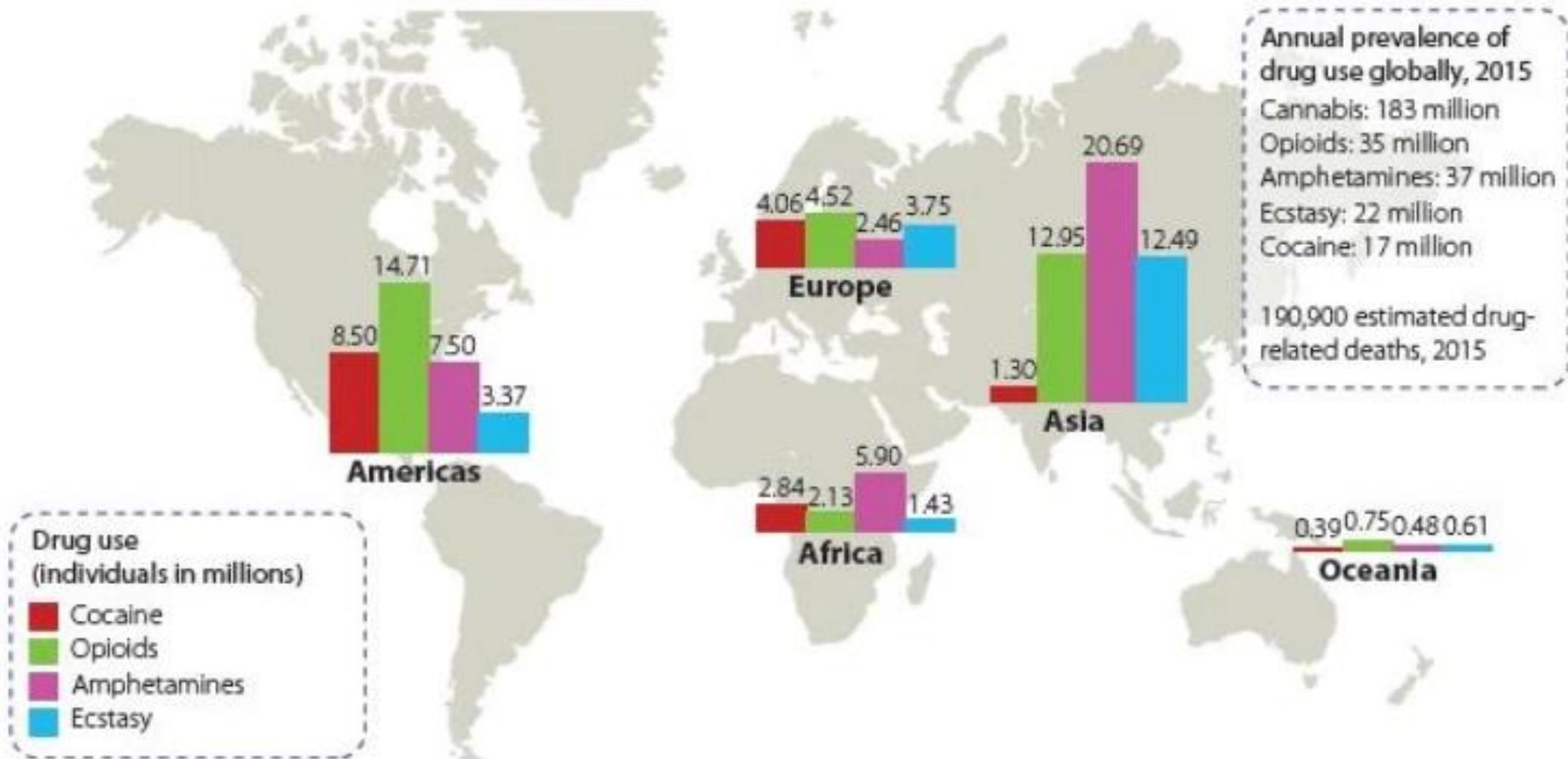
# Drug use in the World



The consumption of substances varies across different regions of the world, influenced by social, cultural, economic, and legal factors. These differences can lead to a diversity in the types of substances consumed and the related problems. Next is an examination of regional differences in drug and alcohol consumption:





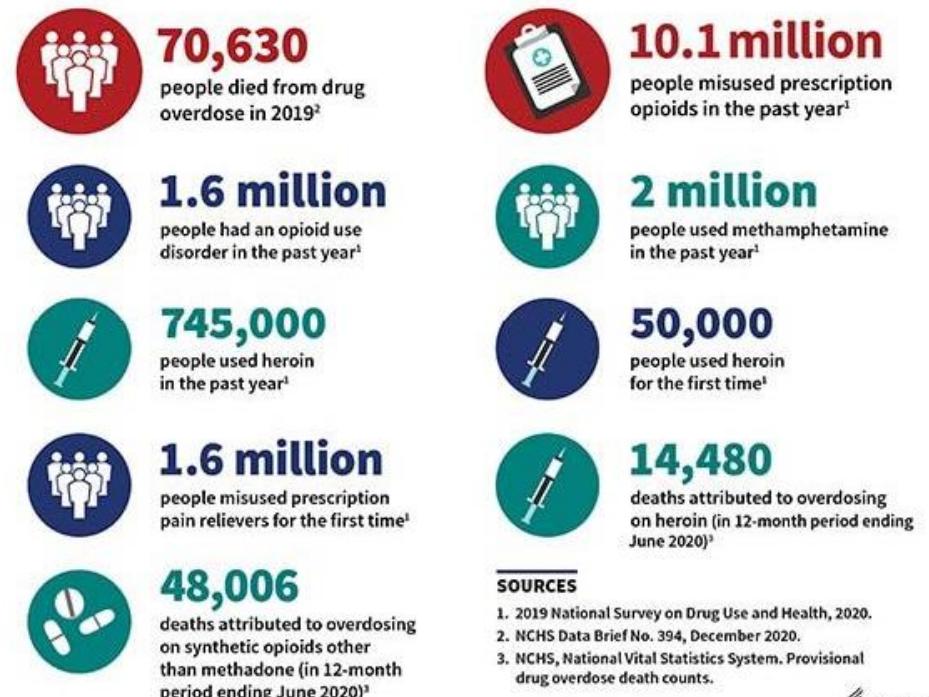


# North America: High Prevalence of Opioid Use

The use of **opioids**, especially synthetic opioids like fentanyl, is extremely high in North America. The opioid crisis in this region has become one of the main public health challenges in recent years. The United States and Canada have the highest rates of opioid overdose deaths. This crisis is largely linked to the prescription of opioid medications, followed by a shift towards illegal opioids.

In addition to opioids, the concurrent use of other drugs such as **cocaine** and **methamphetamine** is also on the rise. These combinations increase the risk of overdose.

## THE OPIOID EPIDEMIC BY THE NUMBERS



### SOURCES

1. 2019 National Survey on Drug Use and Health, 2020.
2. NCHS Data Brief No. 394, December 2020.
3. NCHS, National Vital Statistics System. Provisional drug overdose death counts.

# Europe: High Prevalence of Alcohol and Psychoactive Substances

Alcohol consumption has traditionally been high in Europe and continues to be a major public health issue on the continent. Countries like Russia, the UK, and Scandinavian nations have high rates of alcohol consumption. Also cannabis remains by far the most commonly consumed illicit drug in Europe. The use of psychoactive substances such as ecstasy (MDMA) and cocaine is also common in Europe. These drugs are particularly popular among young people and partygoers. In recent years, cocaine use has been increasing in Western European countries like Spain and the UK.

# Australia: High Consumption of Alcohol and Stimulants

Australia is known for **heavy alcohol consumption** patterns among various demographic groups. Alcohol use is prevalent among both young people and the elderly, associated with issues such as traffic accidents, violence, and alcohol-related health problems.

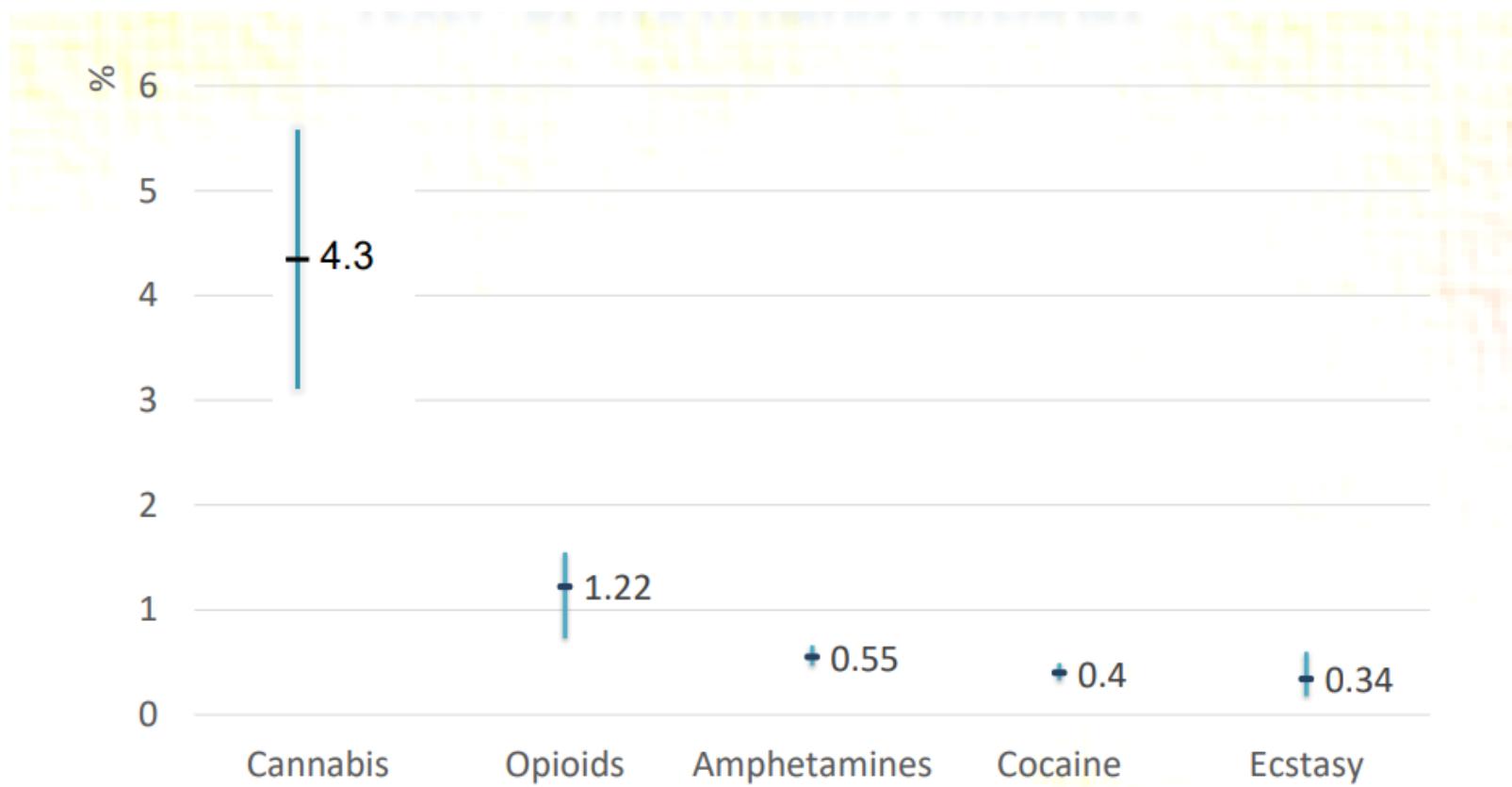
The use of **amphetamines** and **methamphetamine** is also high in Australia. These substances are particularly common among young people and workers who require long hours due to their stimulating effects on the central nervous system.

# Other Regions: East and Southeast Asia, Africa

In East and Southeast Asia, **methamphetamine** use has become one of the largest public health challenges. Due to widespread production and easy access, it is widely consumed.

In Africa, the use of **cannabis** and **homemade alcohol** is common and is associated with various health problems, especially in areas with limited healthcare services.

# Prevalence of drug use in the world

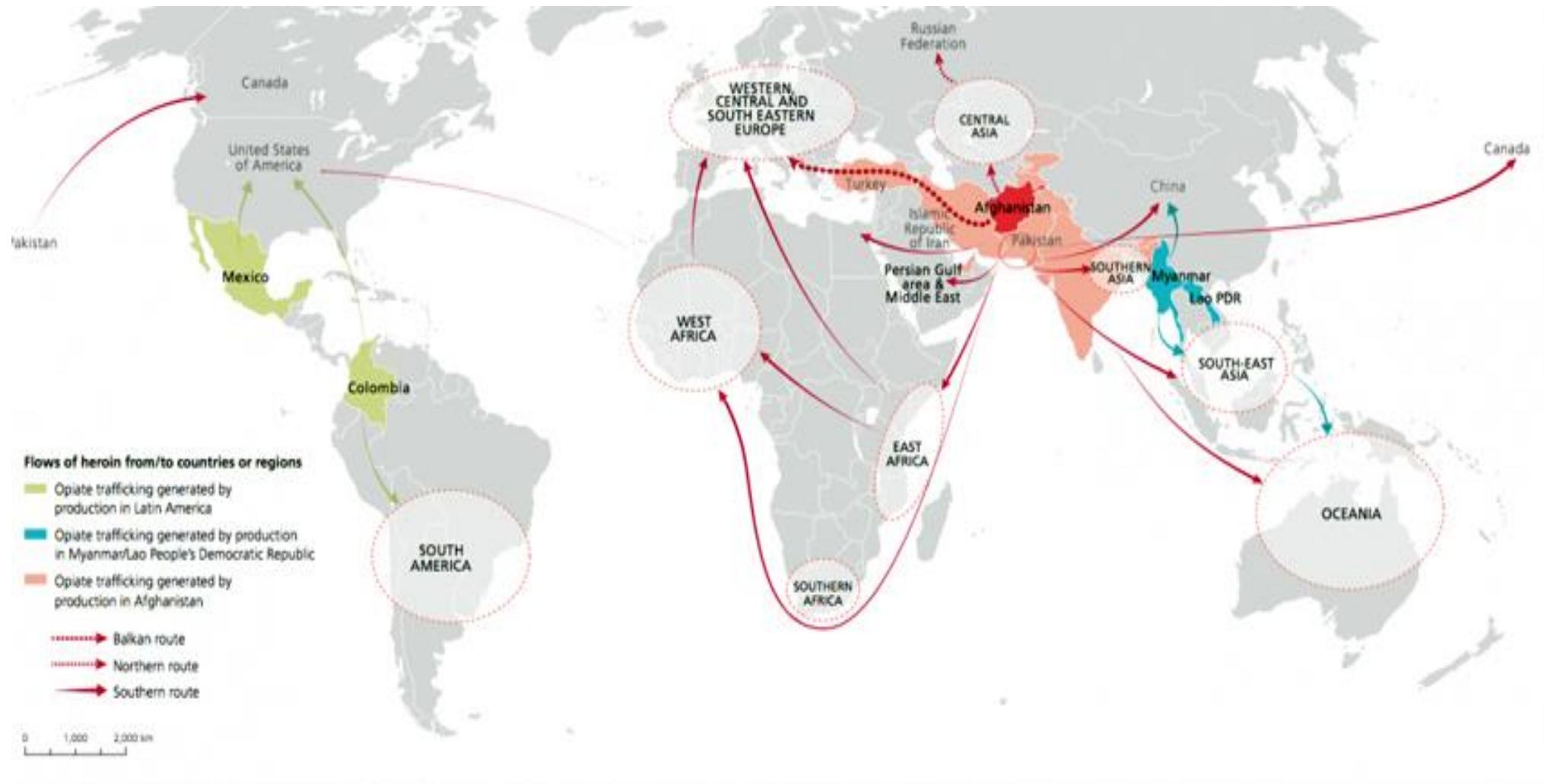


**Global opiate abuse:** 15.6 million people, or 0.4 per cent of the world's population aged 15-64.

- Opiates continue to be the **main problem drug worldwide**, accounting for some 60 per cent of treatment demand in Asia and in Europe.
- Main using countries: Iran, Russia, Afghanistan, China, Pakistan, UK, USA



# Afghanistan and Iran



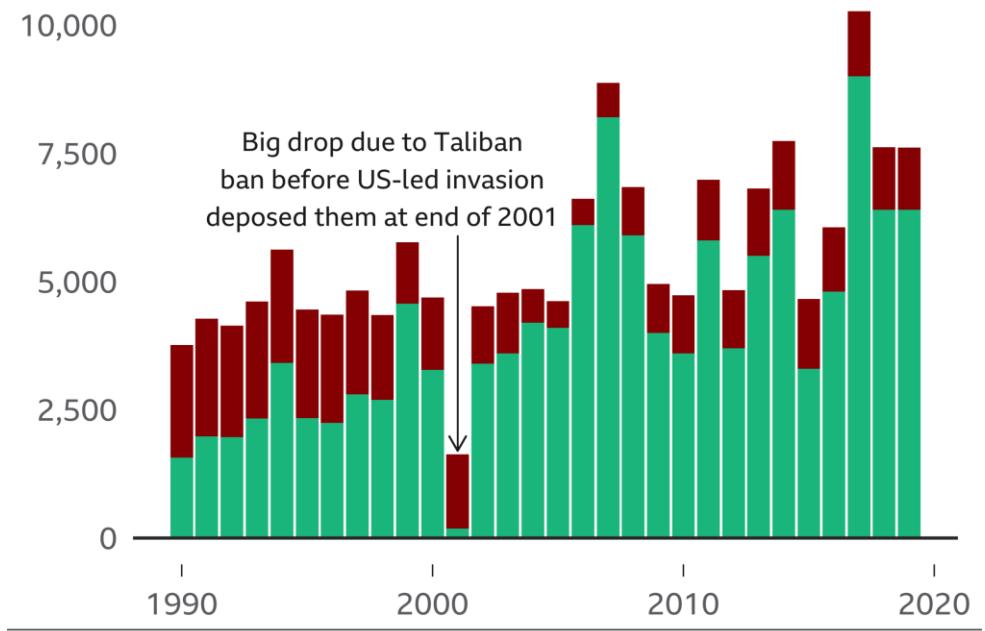
# Taliban effects on opium products



**Afghanistan is responsible for more than 80% of global opium production**

Opium production in tonnes, 1990-2019

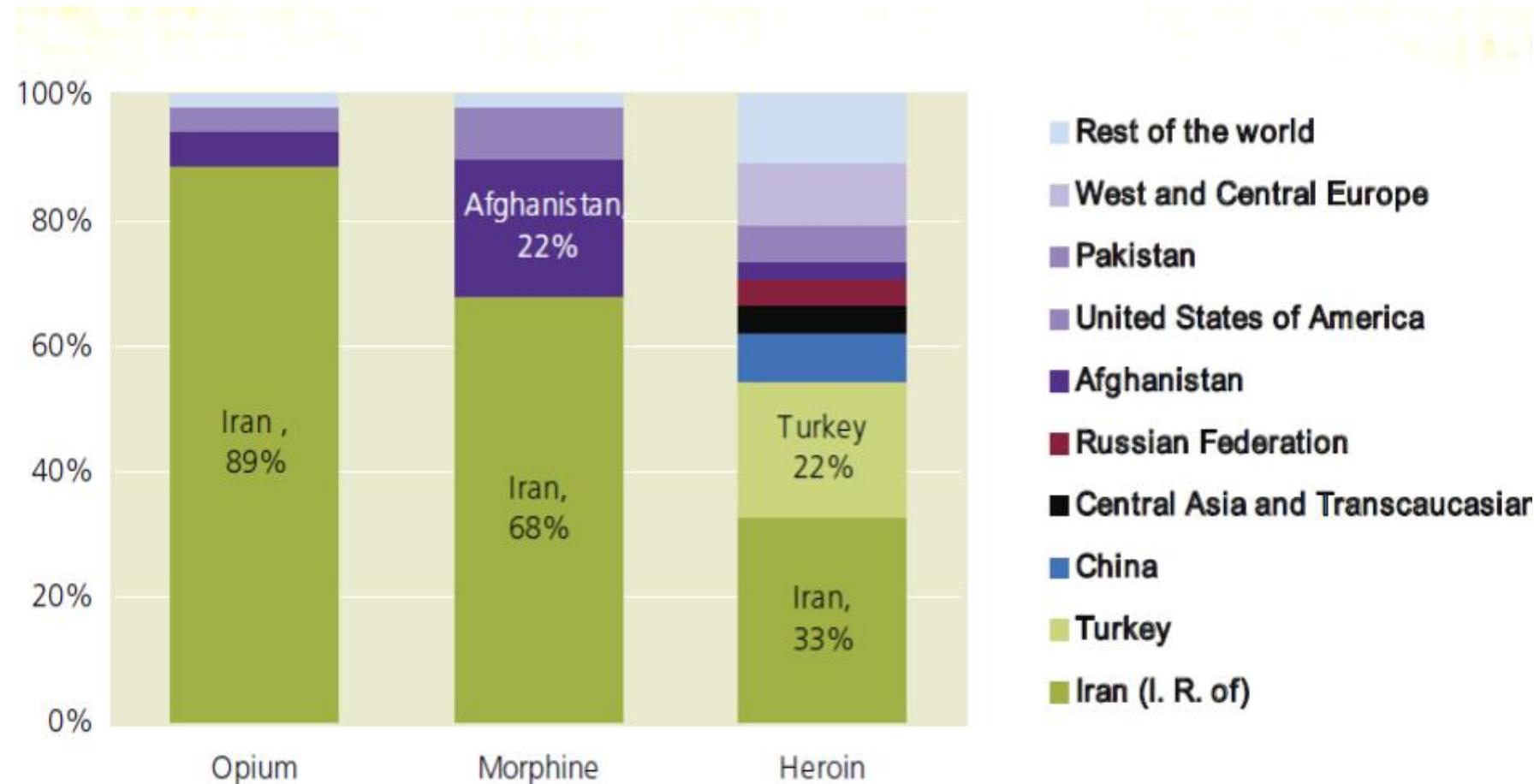
■ Afghanistan ■ Rest of world



Source: UNODC

BBC

# Opium seizure in the world



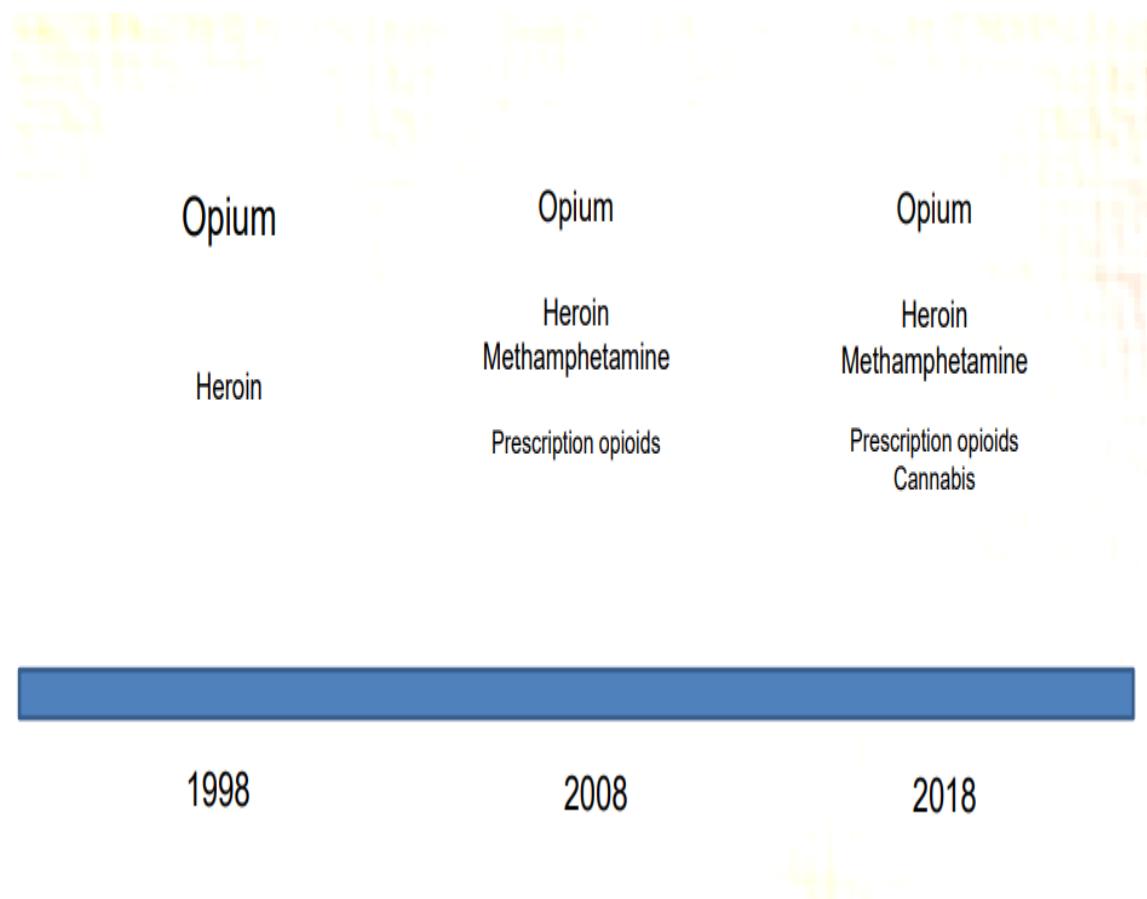
# Opium seizure in Iran



TEHRAN, Nov. 27 (MNA) – The secretary general of Iran Headquarters for Campaign against Drug Trafficking Eskandar Momeni stressed that about 92% of the world's opium discoveries are related to Iran.

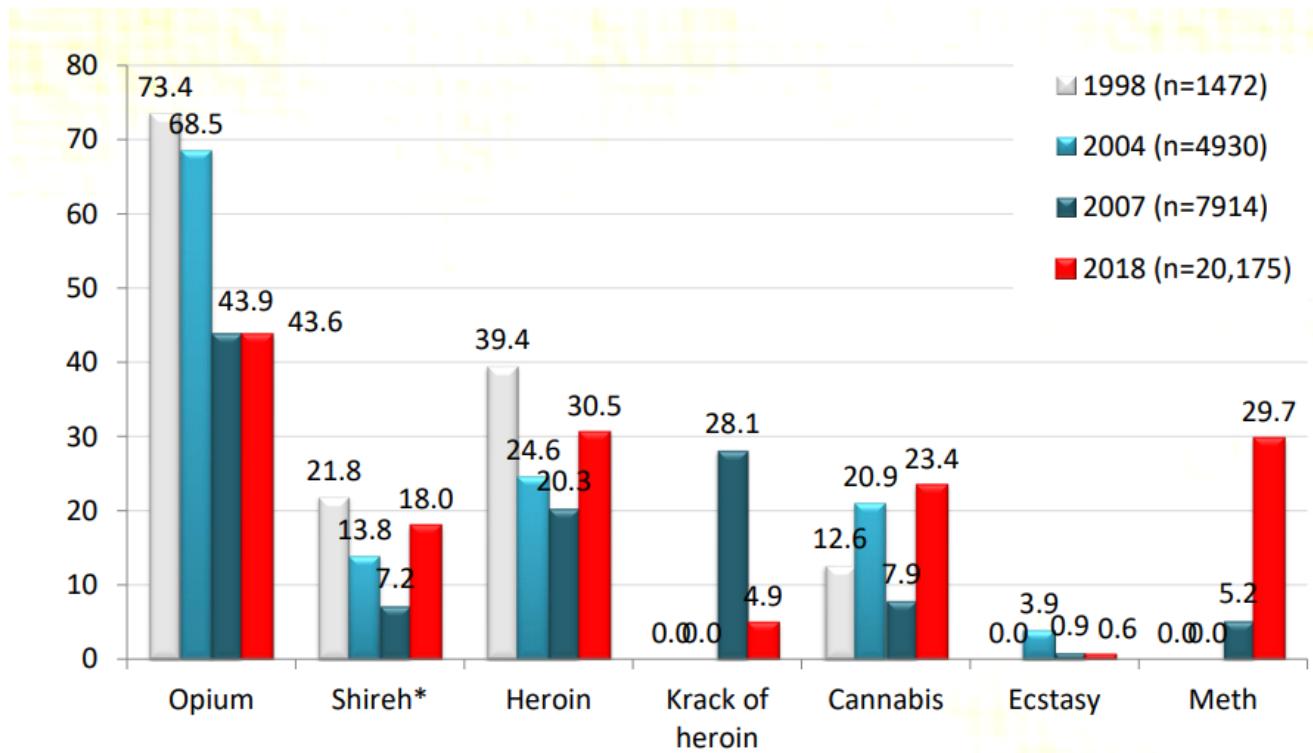
# Iran Addiction Situation

In Iran, addiction to drugs is one of the significant public health challenges. Statistics indicate that over 2 million people in the country suffer from substance use disorders. Opioids, including opium and heroin, are the most commonly used substances in Iran. Additionally, the use of methamphetamine has increased in past years, becoming one of the prevalent stimulant drugs.

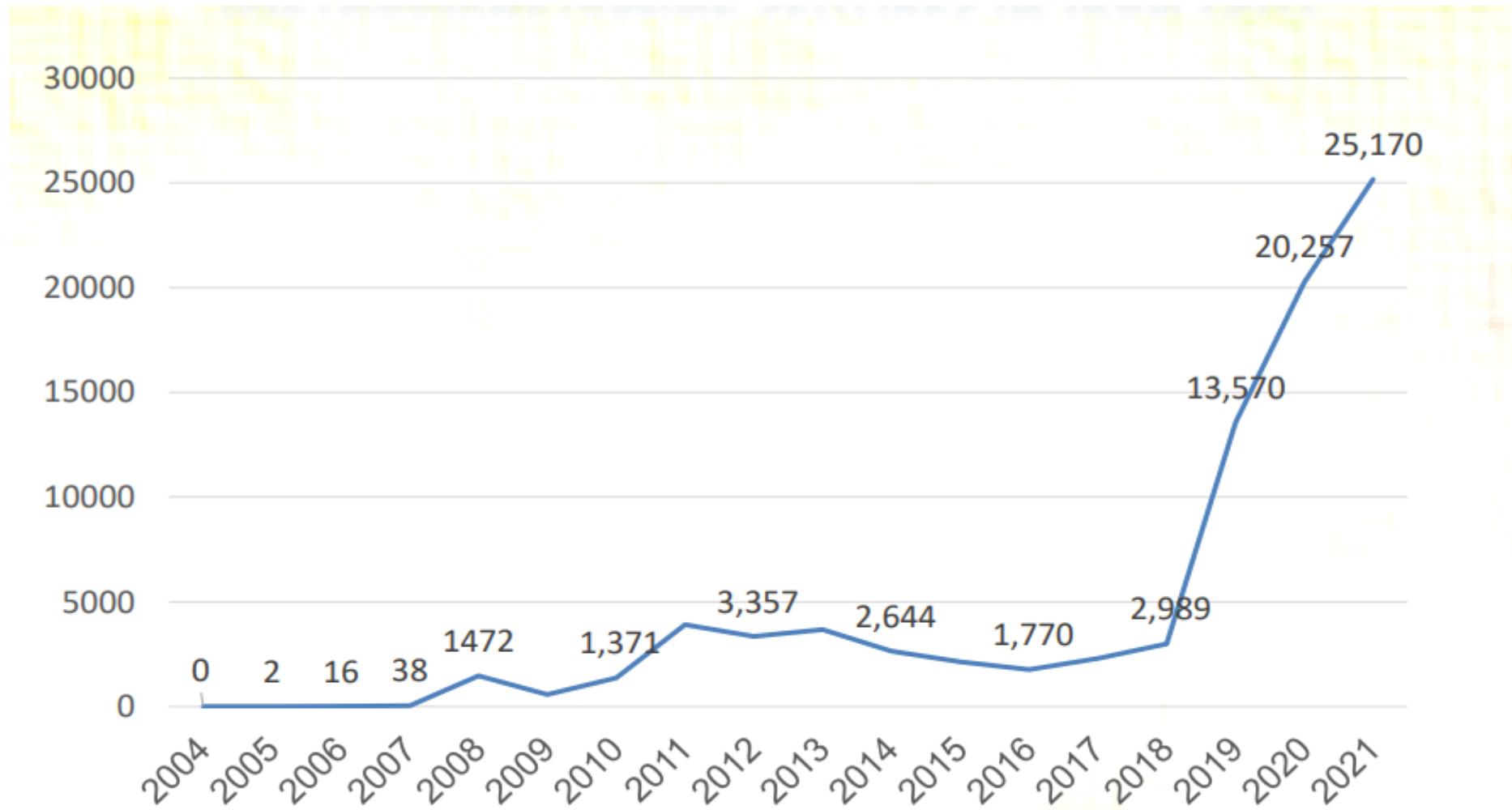


# Iran Addiction Situation

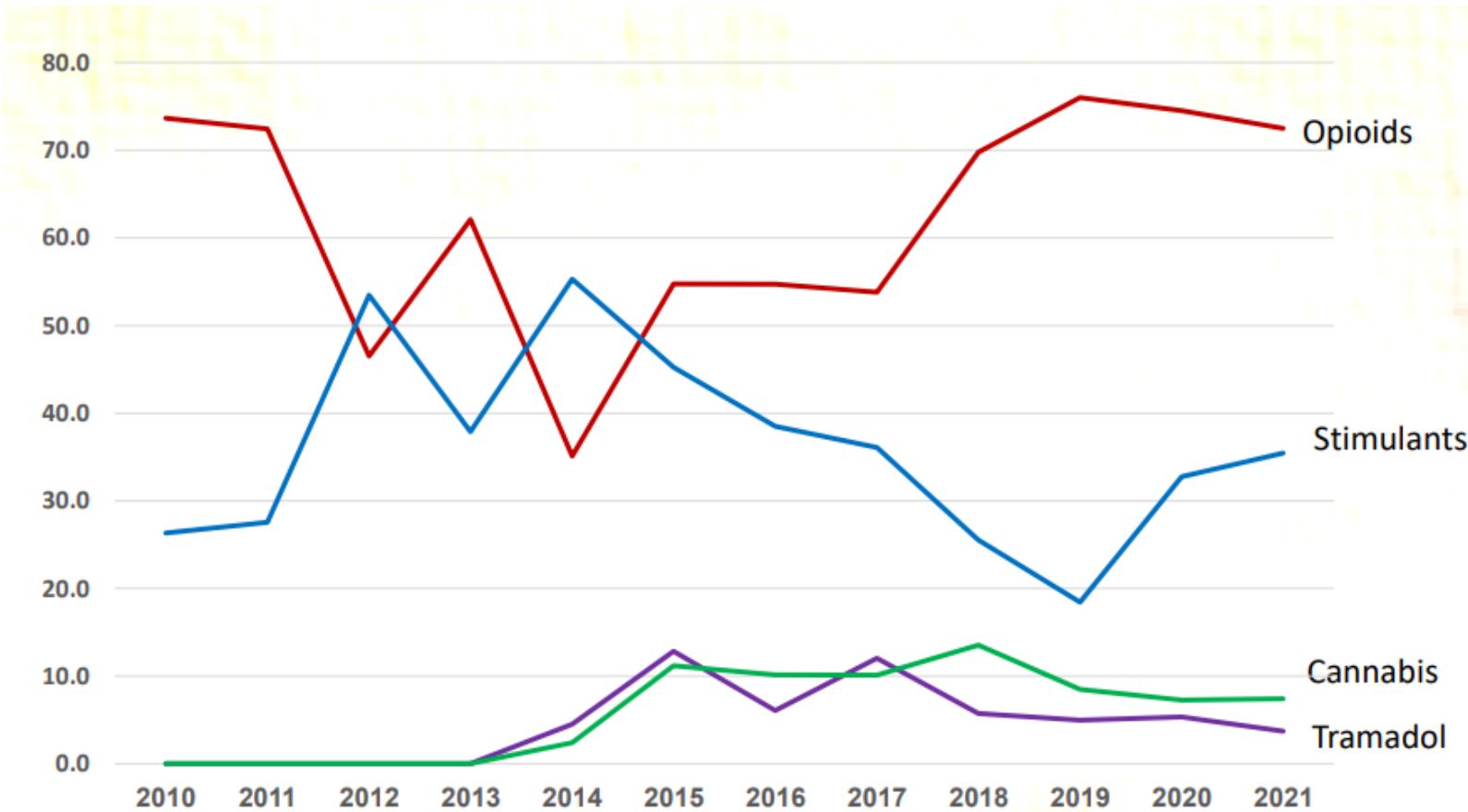
Moreover, patterns of substance use in Iran have changed over time. For example, with increased legal controls and reduced access to opium, some users have turned to synthetic opioids like methadone, as well as stimulants such as crystal meth.



# Methamphetamine Seizures in Iran



# Trends of addiction in Iran



According to internal reports, men are more likely than women to suffer from substance use disorders, with the age group of 20 to 40 years showing the highest prevalence of addiction. Geographically, substance use is higher in marginalized urban areas and rural regions compared to urban centers.



# Studies of addiction in Iran

## General population surveys:

- National Study on drug use in the emergency rooms, 2002
- National household survey on prevalence of substance use and use disorder, cost and service use (IranMHS), 2011
- National household survey on prevalence of substance use, 2015
- Persian Youth Cohort

## National surveys on students:

- School surveys
- University surveys

## Large surveys on drug users:

- Four national survey on drug users 1998, 2004, 2007, 2018
- Survey and qualitative study on IDUs in Tehran, 2001
- Annual statistical reports from treatment centers, since 1996
- Bio-behavioral surveys on IDUs

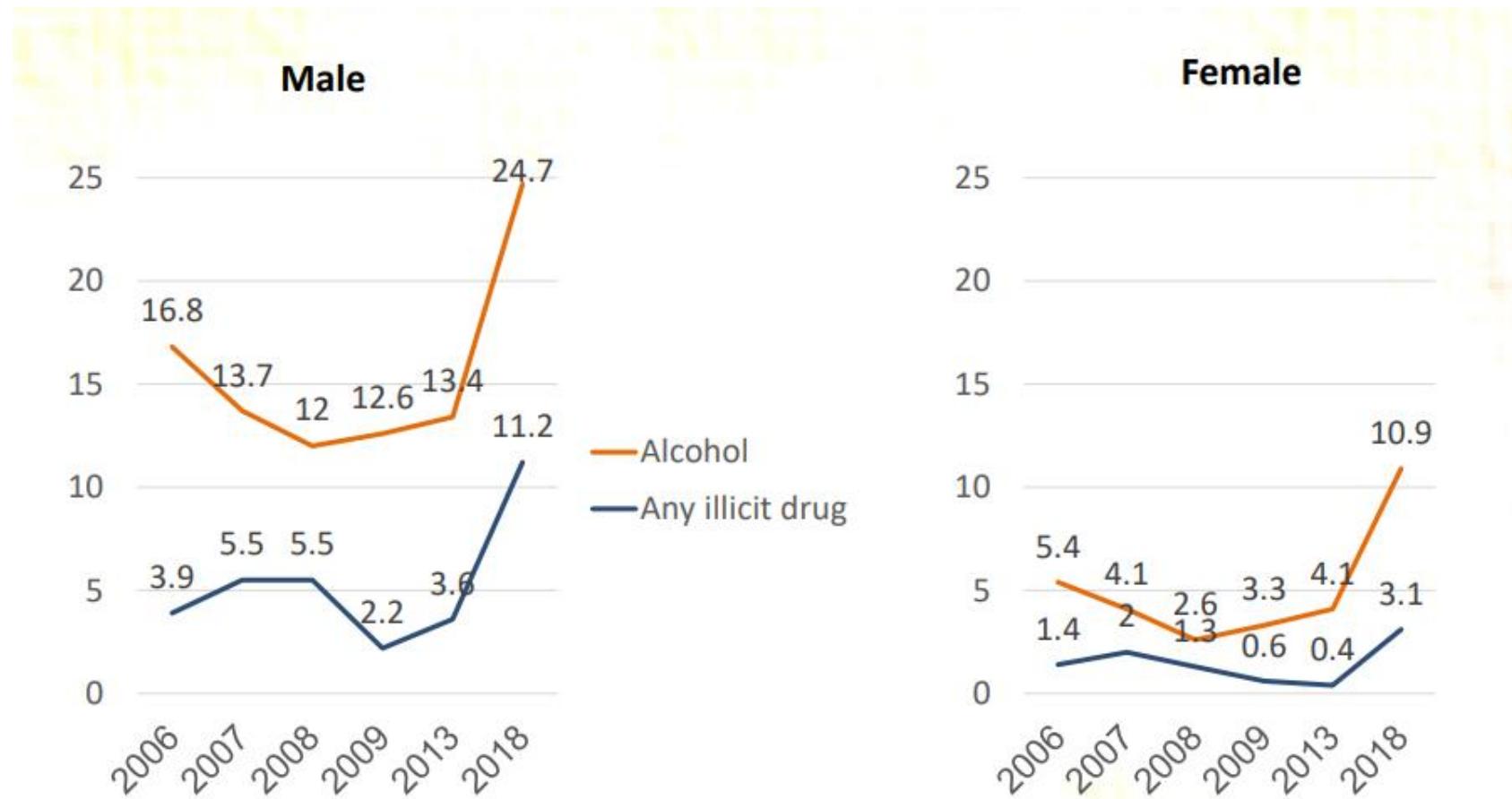
## Other:

- National study on drug use in prisons, 2001
- Study on burden of diseases, 2003, etc.
- Systematic reviews

# National Study

	Current use	Dependence
Opioids	3,761,000	1,158,000
Heroin	277,000	137,000
Alcohol	1,863,000	253,000
Cannabis	391,000	Not estimated

# TUMS students Study



# TUMS students Study

