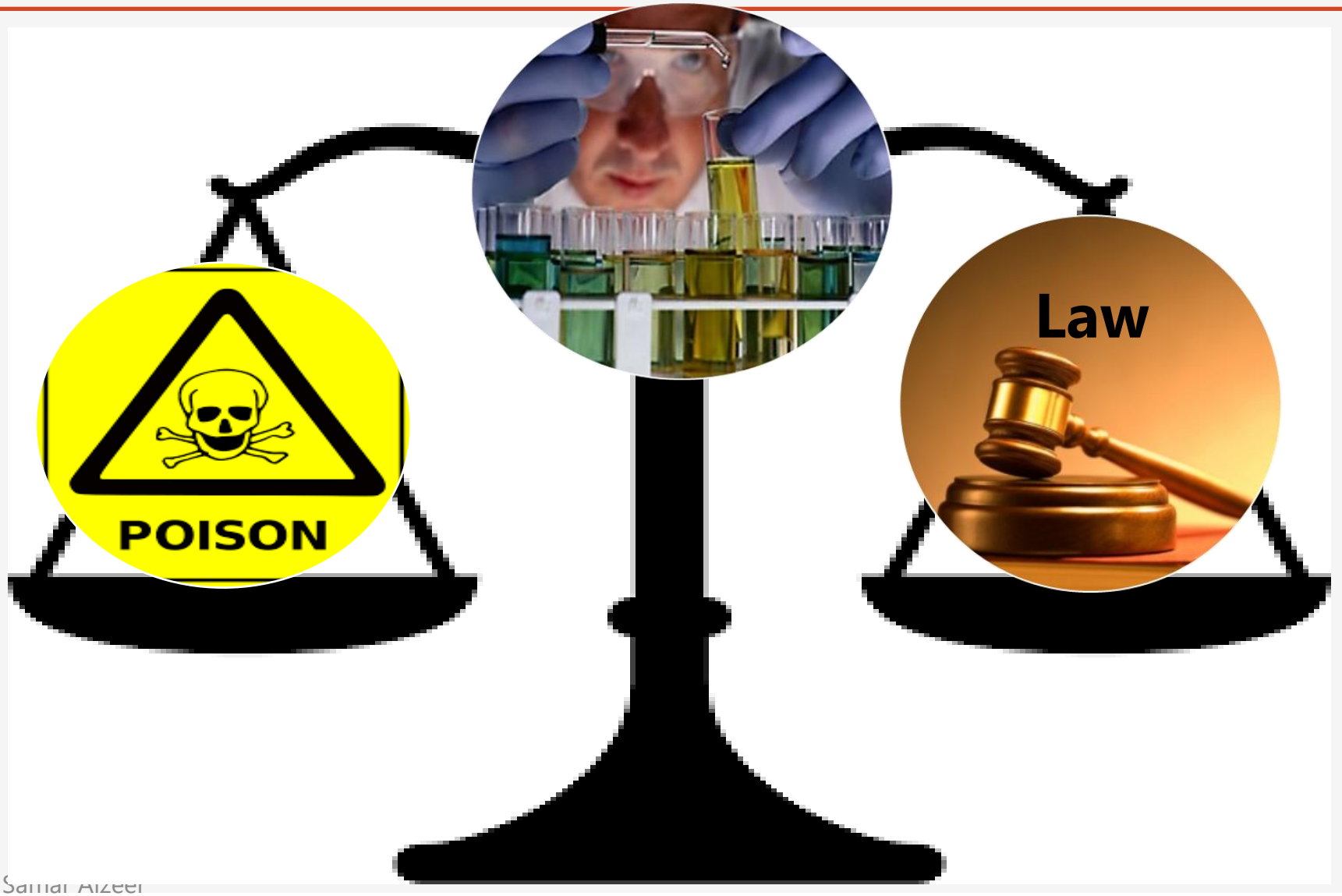
# Forensic Toxicology

## Introduction to Forensic Toxicology

**Dr Samar Alzeer**

# Forensic Toxicology



# Brief History

- **Paracelsus (1493–1541)**

  *"All substances are poisons: there is none which is not a poison. The right dose differentiates a poison and a remedy."*

- **Carl Wilhelm Scheele (1775)**

  *Conversion of As2O3 to Arsine gas in non biological samples*

$$As_2O_3 + 6Zn + 12HNO_3 \rightarrow 2AsH_3 + 6Zn\,(NO_3)_2 + 3H_2O$$

- **Johann Metzger (1787)**

  *Reduction of As2O3 to As by heating with carbon*

$$2As_2O_3 + 3C \rightarrow 3CO_2 + 4As$$

# Brief History

## Orfila 1818

"Father of Toxicology."

*(Traite´ de Toxicologie)*

*A book about toxicology and forensic medicine*

# The Marsh Test *Arsenic in Biological samples*

## James Marsh (1836)

Reaction of Carl Wilhelm Scheele (1775)

↓

Arsine gas ($As_2H_3$)

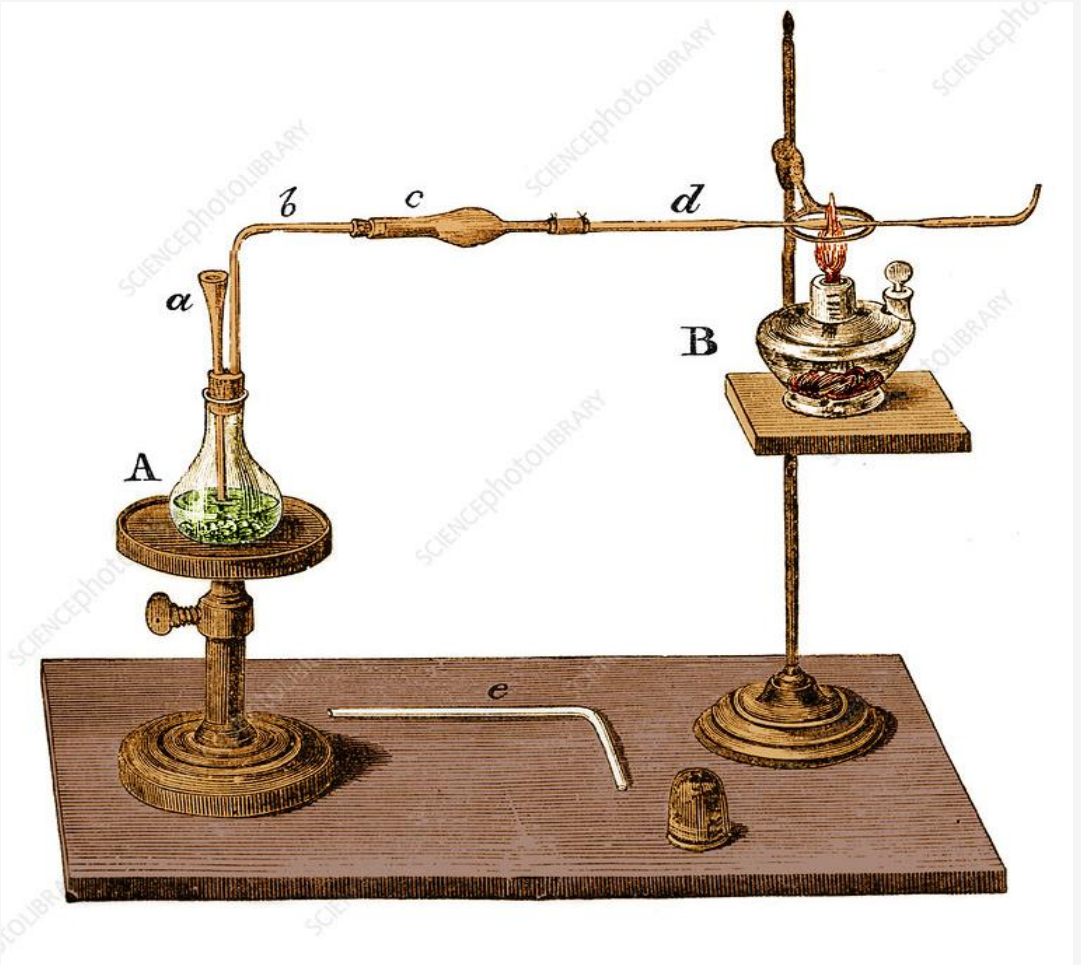
**Heating** ↓

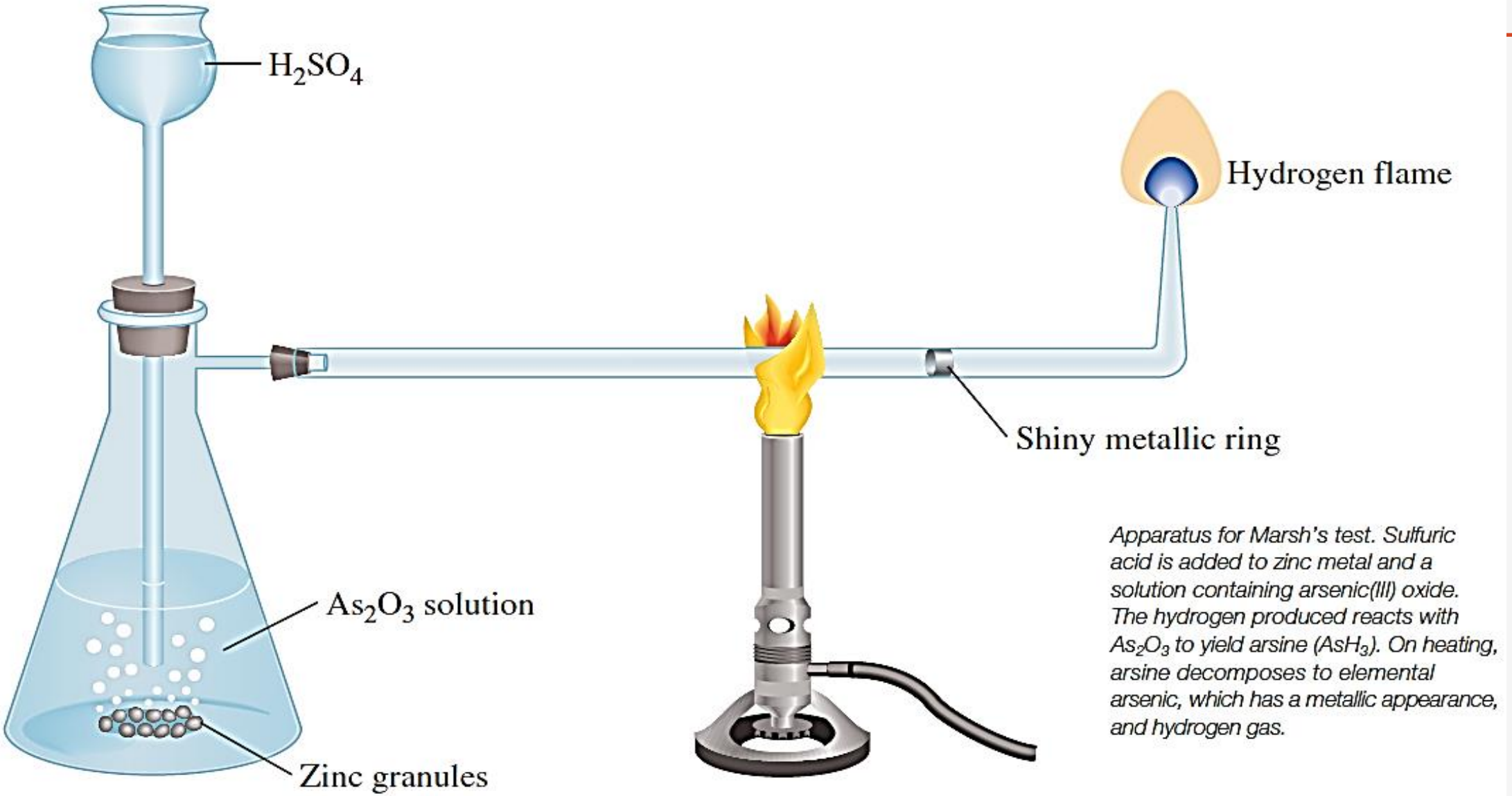
Metallic arsenic

↓

collected on a solid surface such as a glass

↘ ***Arsenic mirror***






*Apparatus for Marsh's test. Sulfuric acid is added to zinc metal and a solution containing arsenic(III) oxide. The hydrogen produced reacts with $As_2O_3$ to yield arsine ($AsH_3$). On heating, arsine decomposes to elemental arsenic, which has a metallic appearance, and hydrogen gas.*

*Marie Cappell*

# THE LAFARGE AFFAIR (1840)

## *The March test*

- Husband Charles LaFarge was poisoned by arsenic
- Arsenic was detected in LaFarge's stomach and stomach contents by outdated method ⟶ not reliable . Then Applied March test and arsenic was not detected

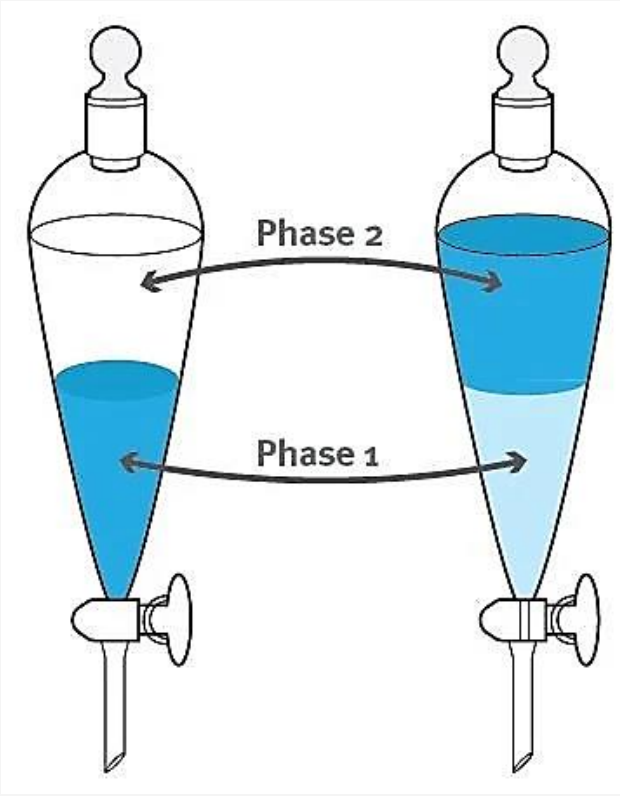
- Orfilla then repeated the March test ⟶ arsenic was detected
- Inconsistency his results was due to lack of expertise in the performance of the March test

# Stas & Otto 1851

## *Extraction of alkaloids from biological samples : The basis for liquid-liquid extraction*

- Liquid –liquid extraction of alkaloids into organic solvents & removal of fats.
  Example : ***Nicotine***

- The substance is digested in alcohol and tartaric acid, the fatty and resinous matters are precipitated with water, the fluid is made alkaline, and the alkaloids are extracted with ether or chloroform.



# The Bocarme case in 1843

*Stas method*

- Killer: The Count de Bocarme´,
- He murdered Gustav Fougnies, the Countess' brother
- Preparation of nicotine from tobacco leaves

# Forensic Toxicology includes

- Post mortem Toxicology — Suspicious death
- Driving under the influence — Traffic accidents
- Performance-enhancing drugs — Sport
- Workplace drug testing

# *The four disciplines of Forensic Toxicology*

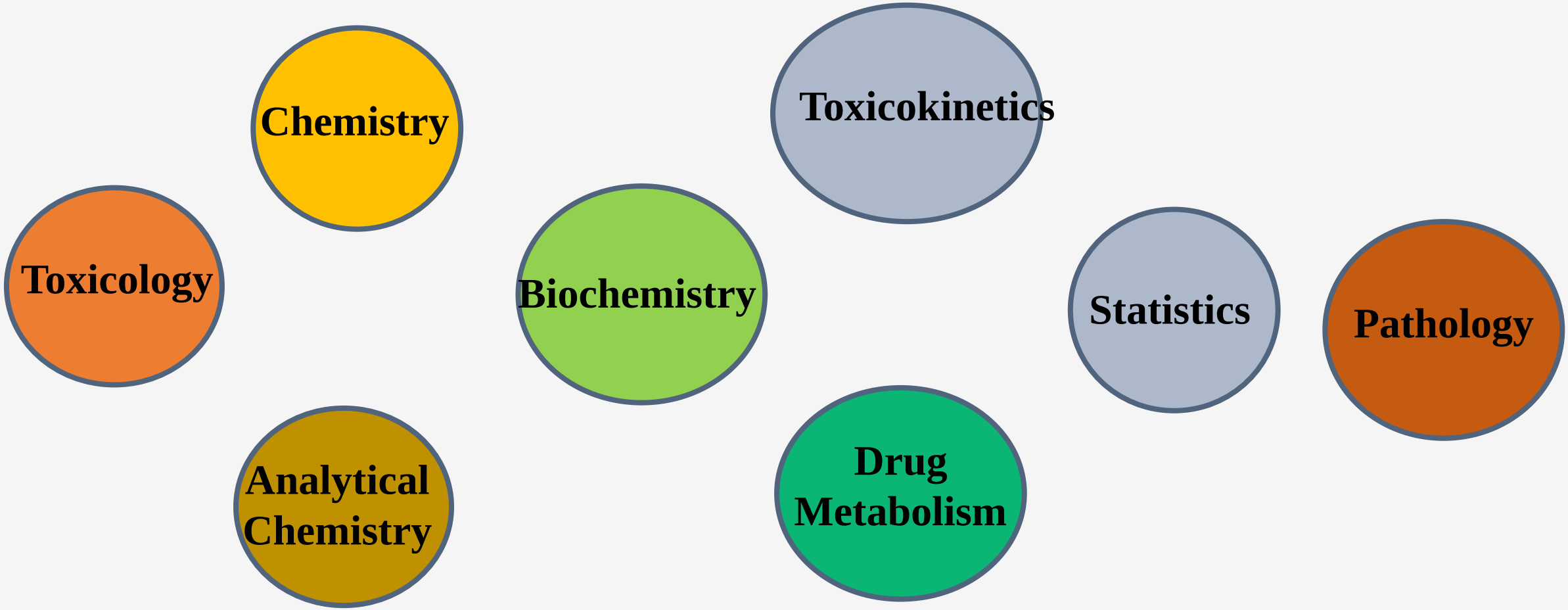
- **Post-mortem Forensic Toxicology**
- **Human –Performance Forensic Toxicology**
- **Doping control**
- **Forensic workplace drug testing**

***The Forensic Toxicology Council, July 2010***

# Forensic Toxicologist should have

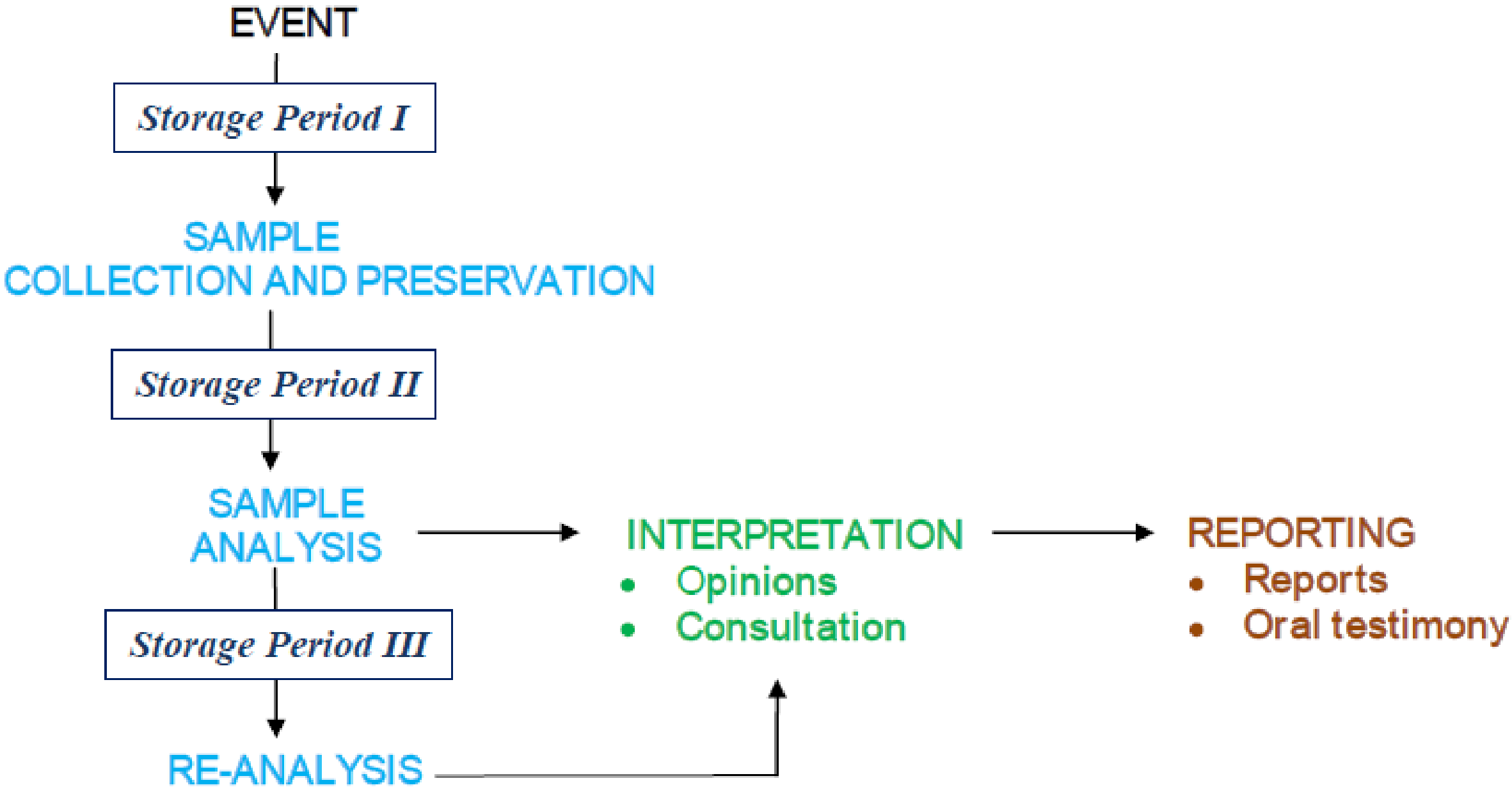
- **Experience**
- **Sufficient knowledge about the case**
- **Sealed & labelled samples**
- **Pure reagents**

# Required Knowledge



# Duties of Forensic Toxicologist

- Registration of samples
- Storage of samples
- Analysis of samples
- Knowledge of substances' characteristics
- Interpretation of results
- Testimony in court


EVENT
Storage Period I
SAMPLE COLLECTION AND PRESERVATION
Storage Period II
SAMPLE ANALYSIS
Storage Period III
RE-ANALYSIS
INTERPRETATION
• Opinions
• Consultation
REPORTING
• Reports
• Oral testimony

# Analytical aspects

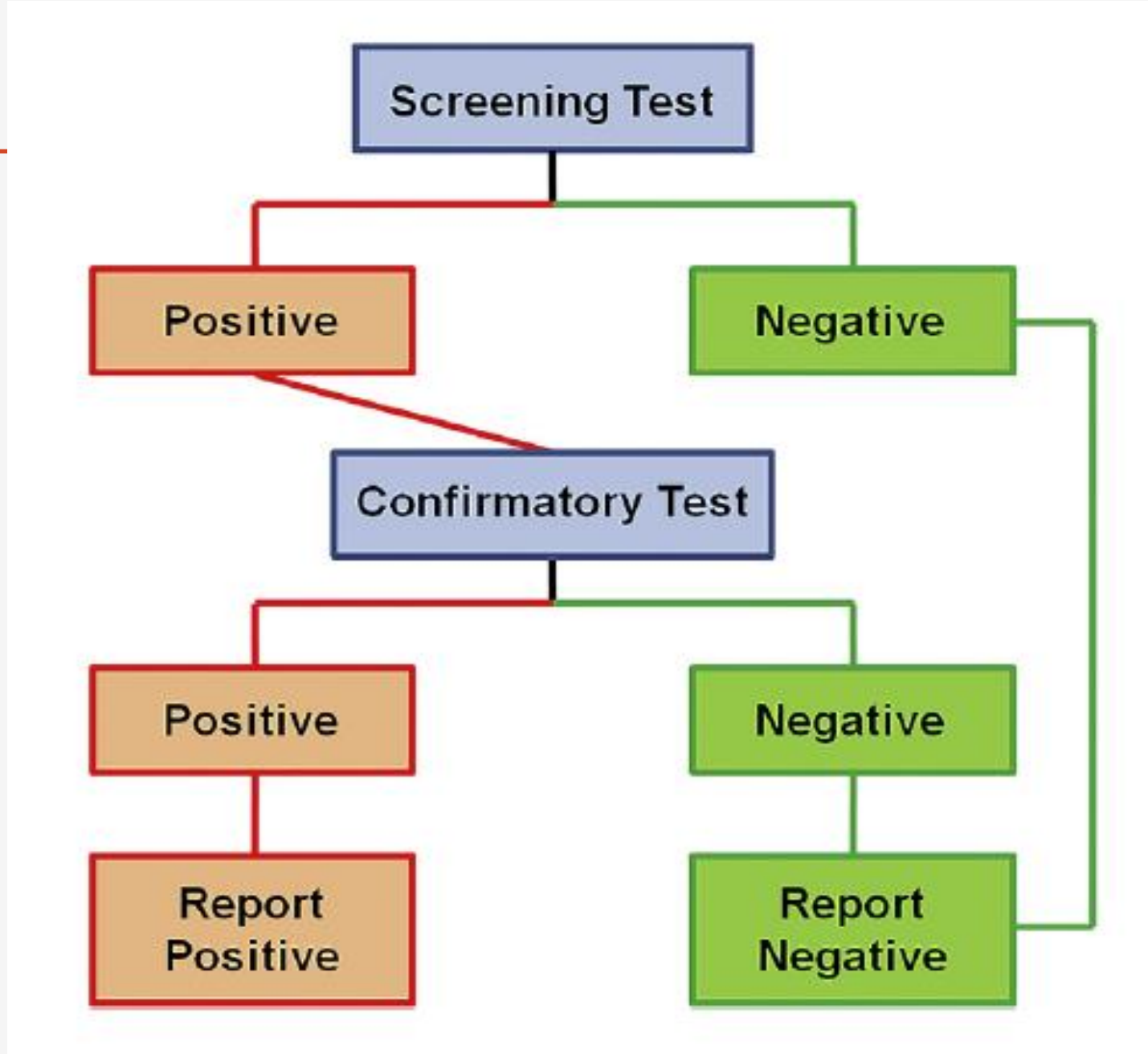
## Screening

- Colour tests
- ELISA

## Confirmation

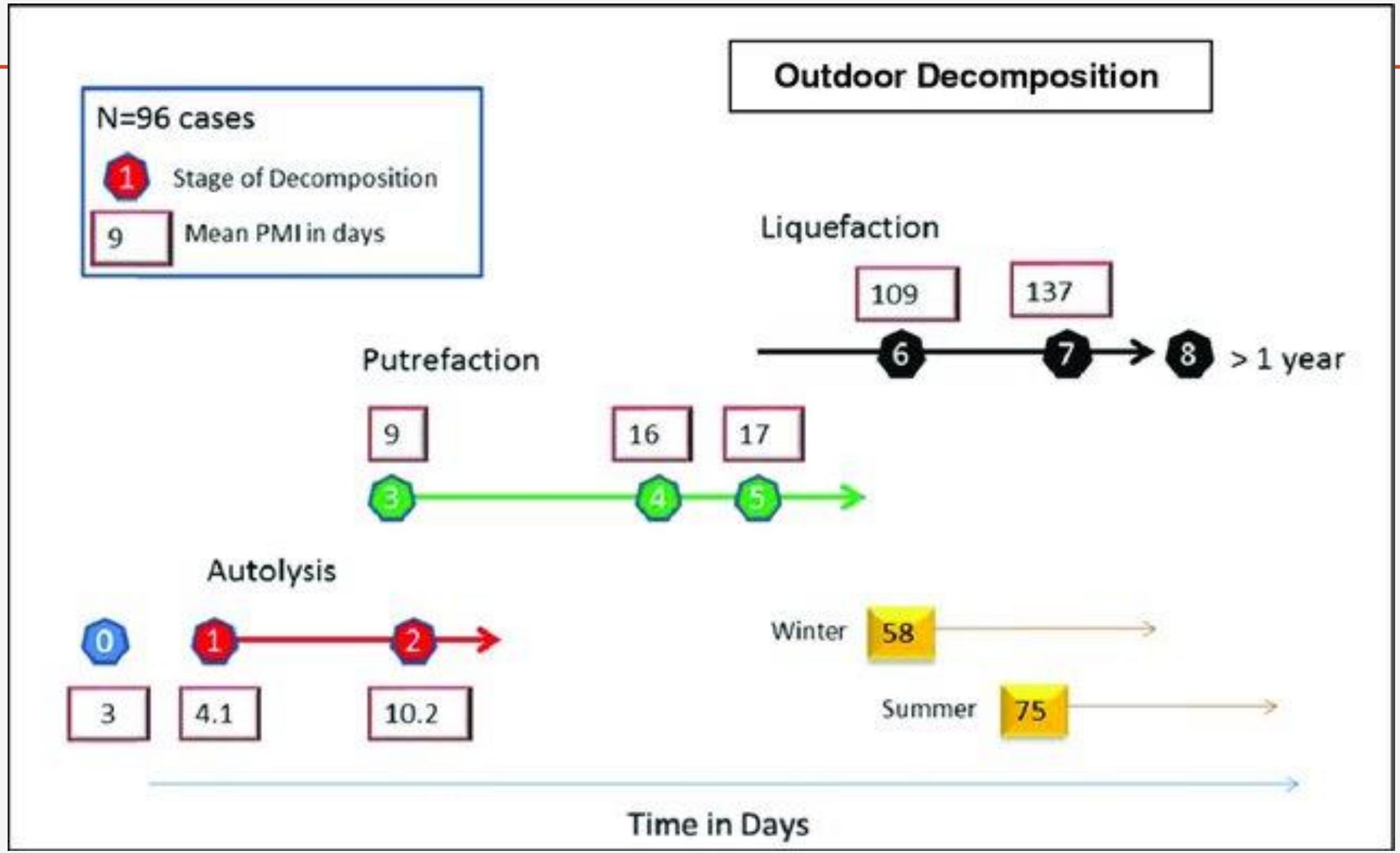
GC/MS
GC/FID
HPLC
LC/MS

The sample may need a derivatisation


Screening Test
Positive
Negative
Confirmatory Test
Positive
Negative
Report Positive
Report Negative

# Determining cause of death or the culprit is not the duty of a forensic toxicologist

1. Positive sample
   - Reason of death
2. Negative sample
   - Sensitivity of reaction
3. Forensic Pathologist


Outdoor Decomposition
N=96 cases
1
Stage of Decomposition
9
Mean PMI in days
Liquefaction
109
137
6
7
8
> 1 year
Putrefaction
9
16
17
3
4
5
Autolysis
0
1
2
3
4.1
10.2
Winter
58
Summer
75
Time in Days

# Post-mortem Toxicology

## Changes after death

### Putrefaction and Autolysis

- **Putrefaction: Effect of bacteria . Wet conditions**

The process by which the soft tissues of the body are converted to gases, liquids, and small molecules by microorganisms, and often insect activity and animal predation

*n*-propanol , Acetaldehyde, Isopropanol, Ethanol

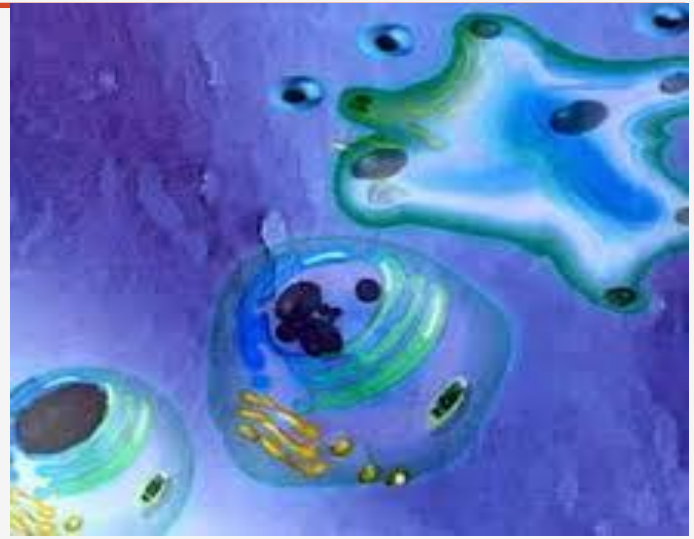
- **Autolysis**

The process by which cells are dissolved by intracellular enzymes

Quicker in stomach and pancreas and in dry conditions

# Post-mortem Toxicology

## Changes after death



- Cease of aerobic respiration → No ATP
- Accumulation of lactic acid → Low pH
- No Na/K pump → Accumulation of Na inside the cells
- Water enters the cell , lysozyme membrane disruption , autolysis

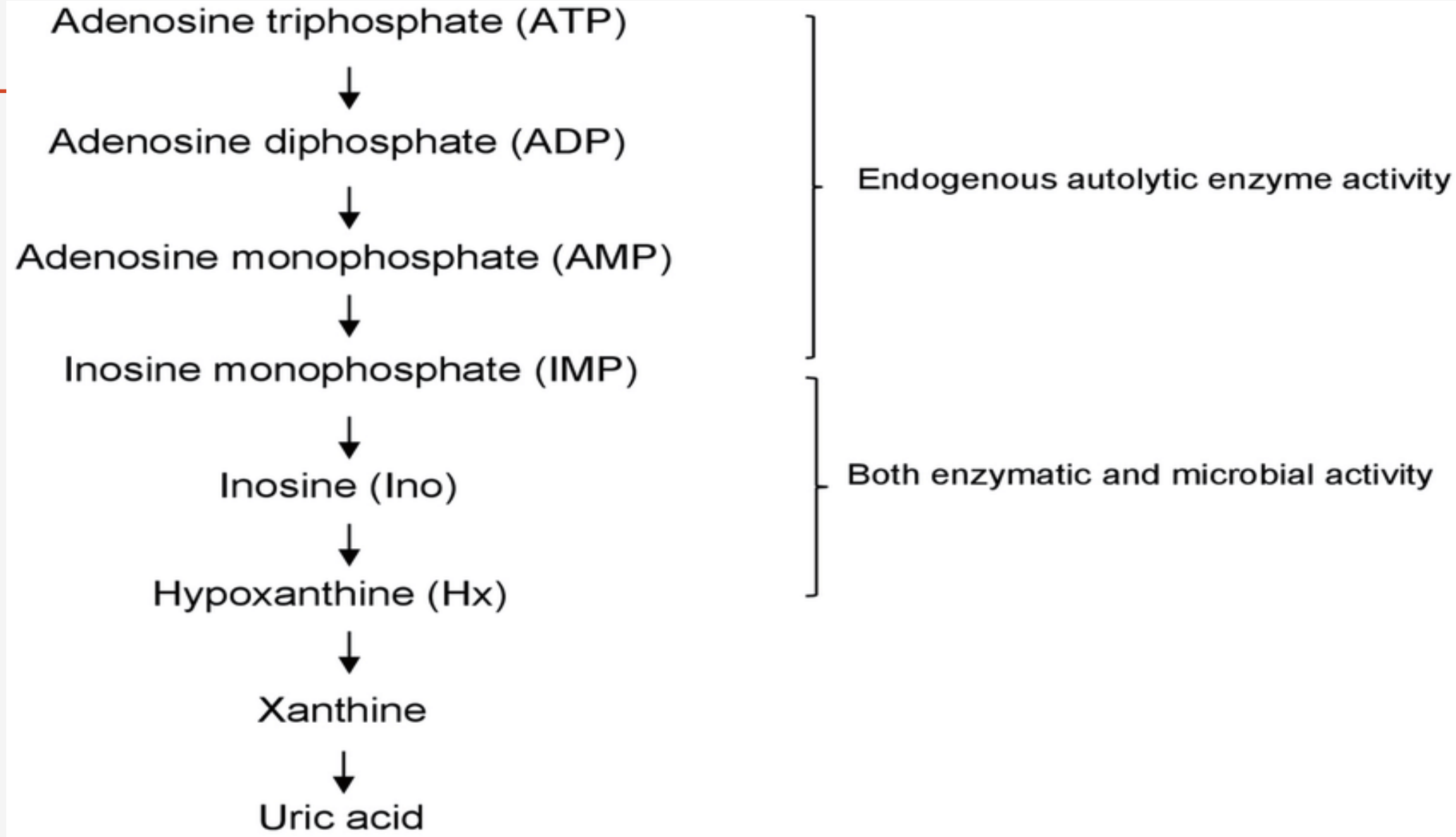
# Post-mortem Toxicology

## Changes after death

- Enzymes such as protease and phosphatase leak into cytoplasm.
- Proteins and drugs that are bound to them leak into extracellular fluid.
- Quicker in Pancreas and stomach.
- Drugs are ionized into the acidic environment and quickly redistributed.

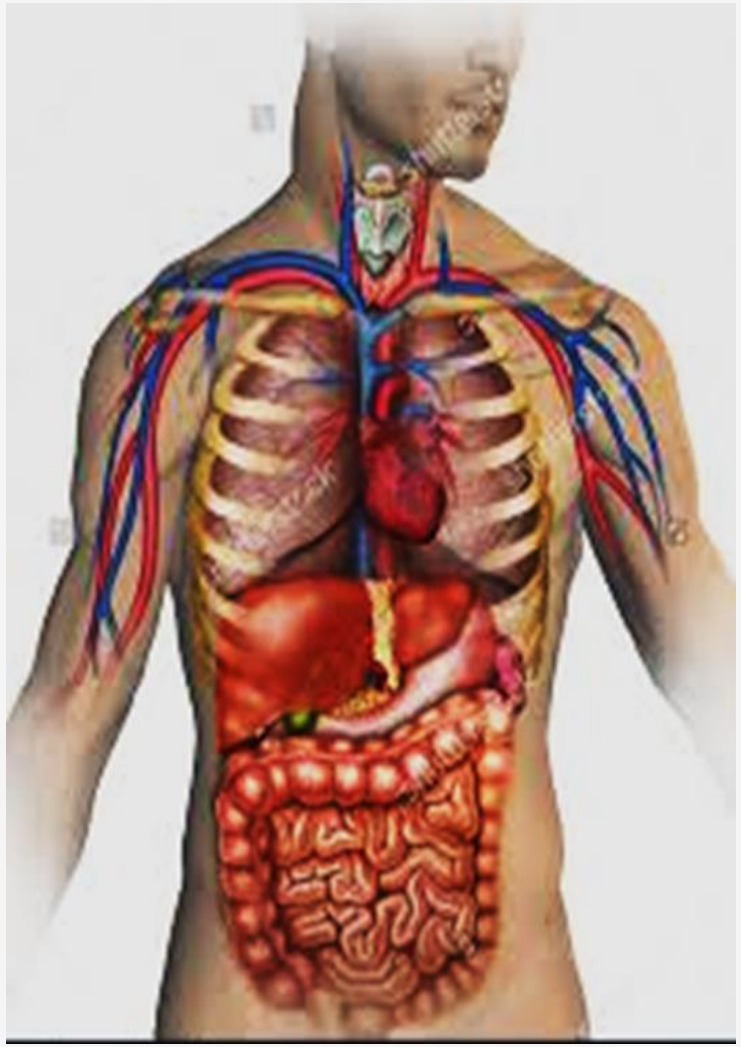
# Putrefaction

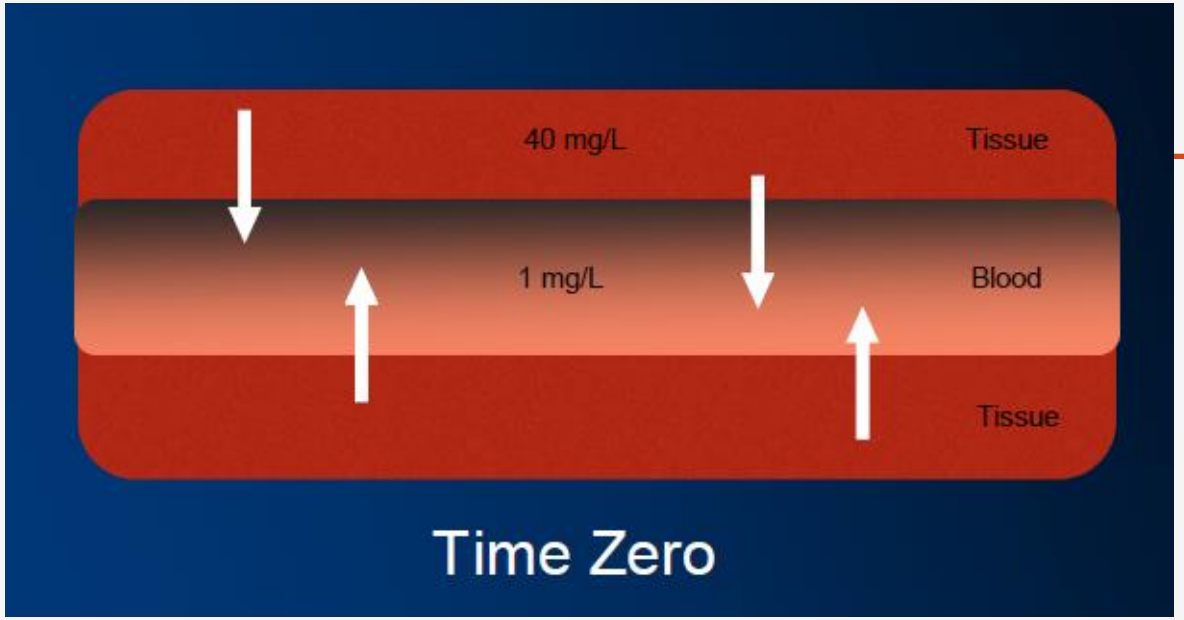
- Microorganisms affect drug concentrations after death
- As putrefaction develops there is an **increase in pH** due to the enzymatic action of microbial enzymes on lipids, carbohydrates, and proteins
- Microorganisms **affect drug concentrations after death**
- Bacteria migrate through the intestinal wall to the blood vessels and lymph nodes
- **Metabolism of drugs , production of ethanol by fermentation**
- The effect of bacteria **decreases at low temperatures**

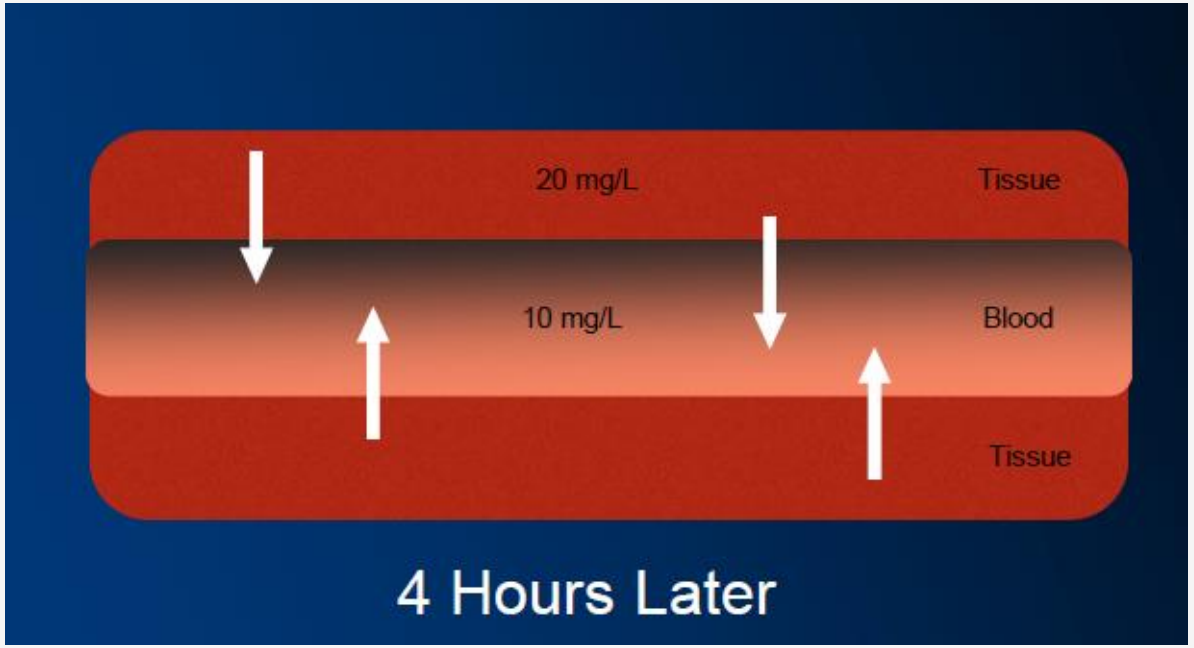

Adenosine triphosphate (ATP)
Adenosine diphosphate (ADP)
Adenosine monophosphate (AMP)
Inosine monophosphate (IMP)
Inosine (Ino)
Hypoxanthine (Hx)
Xanthine
Uric acid
Endogenous autolytic enzyme activity
Both enzymatic and microbial activity

## Post-mortem redistribution

- Redistribution from heart , lungs , left lobe of liver to large blood vessels nearby
- Redistribution of non absorbed drug from stomach to the heart and Inferior vena cava.
- Redistribution of drugs from trachea
- **Happen for basic drugs, which have a large volume of distribution**




40 mg/L
Tissue
1 mg/L
Blood
Tissue
Time Zero


20 mg/L
Tissue
10 mg/L
Blood
Tissue
4 Hours Later

# Post-mortem Toxicology

**Livor mortis postmortem lividity hypostasis**

- The accumulation of fluid or blood in the lower parts of the body or organs under the influence of gravity, as occurs after death

- Irregular blood coagulation and clotting

- Body position may affect redistribution

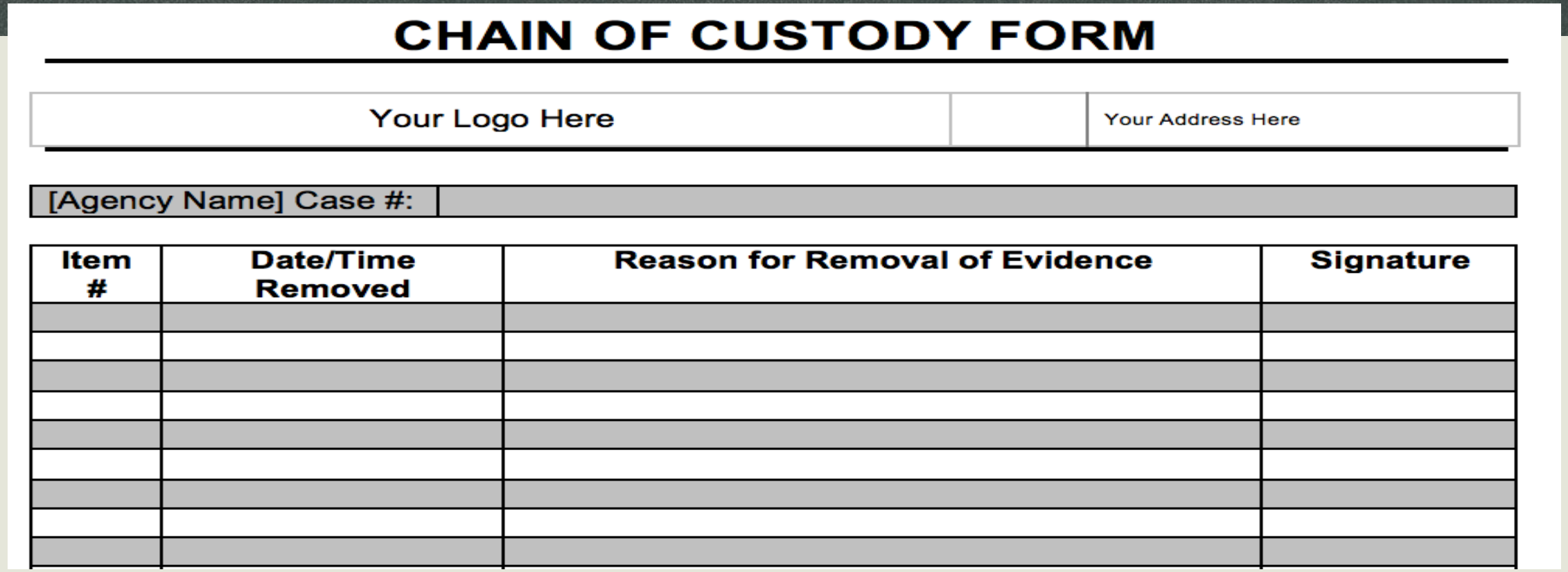
# Post-mortem Toxicology

- Obtain samples quickly , and store them the right way
- Know the limitation of results interpretation
- Regularly review scientific literature in the field

# Samples used for forensic analysis

Dr Samar Alzeer

# Chain of custody



## CHAIN OF CUSTODY FORM

| Your Logo Here | | Your Address Here |
|---|---|---|

| [Agency Name] Case #: | |
|---|---|

| Item # | Date/Time Removed | Reason for Removal of Evidence | Signature |
|---|---|---|---|
| | | | |
| | | | |
| | | | |
| | | | |
| | | | |
| | | | |
| | | | |
| | | | |
| | | | |

Chain of custody (CoC) refers to the chronological documentation or paper trail, showing the seizure, custody, control, transfer, analysis, and disposition of samples

# Ante-mortem Samples (before death)

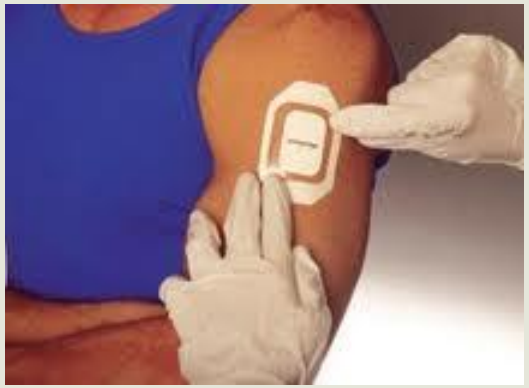
Blood

Urine

Hair

Nail

Saliva



Sweat

Meconium (New born Faeces )

# Post-mortem Samples (after death)

# GOVERNMENT OF THE DISTRICT OF COLUMBIA
# OFFICE OF THE CHIEF MEDICAL EXAMINER

★ ★ ★

1910 Massachusetts Avenue, S.E., Bldg. 27
Washington, D.C. 20003
Telephone: 202-698-9059 Fax: 202-698-9104

## TOXICOLOGY REPORT ☑ SUPPLEMENTAL

### CASE IDENTIFICATION

| | |
|---|---|
| Toxicology Number | **TX10-1234** |
| Name: | MOHAMMED, Ali Ahmed |
| Report Date: | 11/8/2010 |
| Agency Name: | OCME |
| Agency Number: | **10-02311** |
| Medical Examiner: | Lois R. Goslinoski, M.D. |

### SPECIMEN(S) RECEIVED

| Item | Sample | Date Received |
|---|---|---|
| 1 | Femoral - Blood | 10/18/2010 |
| 2 | Femoral - Blood | 10/18/2010 |
| 3 | Heart - Blood | 10/18/2010 |
| 4 | Heart - Blood | 10/18/2010 |
| 5 | Urine | 10/18/2010 |
| 6 | Bile | 10/18/2010 |
| 7 | Vitreous Humor | 10/18/2010 |
| 8 | Liver | 10/18/2010 |
| 9 | Brain | 10/18/2010 |
| 10 | Gastric Contents | 10/18/2010 |

### RESULTS

| Item Sample | Compound | Method 1 | Method 2 | Value | Units | Comments |
|---|---|---|---|---|---|---|
| 2 - Femoral - Blood | Ethanol | HS/GC-1 | HS/GC-2 | 0.20 | g/100mL | |
| 7 - Vitreous Humor | Ethanol | | HS/GC-2 | 0.22 | g/100mL | |

ELECTROLYTE PANEL RESULTS

# Selection of samples

- Ease of use
- Ease of specimen collection
- Presence of interferences
- Matrix effects
- Parent drug and/or metabolites
- Detection time
- Stability of the drug(s) in the specimen
- Putrefaction
- Potential for automated analysis
- Sample volume
- Indication of short-term or long-term drug use
- Reference data
- Interpretive value

# Collection of samples

- **Glass containers** are preferable:
  inert , no contaminants ,larger volume . Better for gases & volatile substances

- Containers of 50 ml Volume are good for blood and urine

- Disadvantage: breakage , also organic analytes may be adsorbed onto the glass surface

- Trace elements may be desorbed from the glass into the sample, thus increasing the concentrations of Zn , Cd , Cu , Hg in the sample

# Collection of samples

- **Plastic containers** are good for solid samples and gastric contents.
- have the benefits of being both disposable and more resistant to breakage than glass containers.
- Disadvantage: Problem of adsorption for highly lipid-soluble analytes.
- If plastic containers are chosen, their integrity at low temperatures should be evaluated. **Polystyrene** is more susceptible to cracking at frozen temperatures than **polypropylene** vessels

# Collection of samples

- Containers of 50 ml Volume are good for blood and urine
  - Excessive headspace in the container can increase the chance of oxidative loss, volatilisation of analyte
  - Containers for blood samples have already a preservative / anti-coagulant substance
  - Routine analysis for long-preserved (old) negative samples
  - Care must be taken for drugs that undergo photodecomposition by preventing exposure to sunlight or artificial light

    Example: **LSD , benzodiazepines (Clonazepam, lorazepam, nitrazepam)**
  - Sample labelling

# Quantities of Ante-mortem samples

| Antemortem | |
|---|---|
| **Specimen** | **Quantity** |
| Blood | 10–20 mL |
| Urine | 25–100 mL |
| Amniotic fluid | 5–30 mL |
| Breast milk | 10–20 mL |

| | |
|---|---|
| Meconium | All |
| Hair | Pen-size lock |
| Saliva | 1–5 mL |
| Sweat | Microlitres (insensible sweat); 1–5 mL (sensible sweat) |

# Quantities of post-mortem samples

| Postmortem | |
|---|---|
| **Specimen** | **Quantity** |
| Blood, heart | 25 mL |
| Blood, peripheral | 10–20 mL |
| Urine | All |
| Bile | All |
| Vitreous humour | All |
| Cerebrospinal fluid | All |
| Gastric contents | All |

| | |
|---|---|
| Liver | 50 g |
| Kidney | 50 g |
| Spleen | 50 g |
| Brain | 50 g |
| Lung | 50 g |
| Hair | 50 g Pen-size lock (150–200 hairs or 50 mg) |

# Blood sample/ ante-mortem

## Advantages

- Recent use of drugs: hours/days
- Concentrations are related to physiological effects
- Not easy to be manipulated
- Lots of reference data

## Disadvantages

- Short window of detection
- Collected by an expert

# Blood sample

## ➢ Storage :

4 °C for short storage

-20 ° C for longer storage, and confirmation tests. Stops bacteria growth

## ➢ Preservatives:

**Sodium fluoride: 2% w/v.**

Inhibits enzymatic reactions like: conversion of glucose to ethanol, oxidation of ethanol, esterification of cocaine, losing of some esters like 6 mono acetylmorphine

- Prepare two samples: preservative & non preservative

## ➢ Anticoagulants

Potassium oxalate , sodium citrate , EDTA. 5 mg/ml

Can affect reaction if the volume of sample is so small


KANGSHI
VACUUM TUBE
ESR
2.4 ml
KANGSHI
VACUUM TUBE
EDTA
K2 EDTA
2 ml
KANGSHI
VACUUM TUBE
PLAIN
5 ml
KANGSHI
VACUUM TUBE
Heparin
5 ml
KANGSHI
VACUUM TUBE
GLUCOSE
6 ml
KANGSHI
VACUUM TUBE
SERUM
5 ml
KANGSHI
VACUUM TUBE
SSGT
5 ml
KANGSHI
VACUUM TUBE
PT TUBE
1.8 ml

| Classification* | Items | Additive | Color▲ | Tube Materialr | Main Intended Use | Basic Tube size (mm) |
|---|---|---|---|---|---|---|
| Serum Tube | No Additive Tube | / | | Glass | Determinations in serum for clinical biochemistry, immunology, and serology | Φ13×75/100 Φ16×100/125 |
| | Pro-coagulation Tube | Clot Activator | | Glass/Plastic | | |
| | Gel&Clot Activator Tube | Gel & Activator | | Glass/Plastic | | |
| Plasma Tube | Glucose Tube | Potassium oxalate/Sodium fluoride or EDTA /Sodium fluoride | | Glass/Plastic | Determinations in stabilized anti-coagulated whole blood or plasma for glucose and lactate testing | Φ13×75/100 |
| | PT Tube | 0.109mol/LSodium Citrate 0.129mol/L Sodium Citrate ( 1:9 ) | | Glass/Plastic | Determinations in citrated plasma for coagulation testing | Φ13×75/100 |
| | Heparin Tube | Lithium Heparin, Sodium Heparin | | Glass/Plastic | Determinations in heparinised plasma for clinical chemistry | Φ13×75/100 Φ16×100 |
| Whole Blood Tube | EDTA Tube | EDTA.K2 EDTA.K3 | | Glass/Plastic | Determinations in EDTA whole blood for hematology | Φ13×75/100 |
| | ESR Tube | 0.109mol/L Sodium Citrate ( 1:4 ) | | Glass | blood cell sedimentation rate test | Φ9×120 Φ13×75 |
| | | | | Plastic | | Φ13×75 |

# Blood sample- Post-mortem

**Cardiac blood (right): 50 ml**

**Peripheral blood (femoral) : 10 ml**

- pH decreases after death because of formation of lactic acid
- Whole blood is better than plasma and serum. Contains 60-90% of water

Problems: Possibility of haemolysis

Post-Mortem redistribution

- Calculate percent of parent drug to metabolites: acute poisoning

# Urine sample

- Used in doping in sport . Routine analysis for addicts
- Collected either personally, by catheter in case of unconsciousness , or by inserting a needle in the bladder in case of death.
- Register colour, smell, density, pH

- **Window of detection** : longer than blood
- Concentration of parent drug is usually very small comparing to metabolites

# Urine sample in routine analysis

**Urine sample can be manipulated**

- Dilution of sample
- Adding oxidation agents such as nitrate
- Adding substances that affect pH
- Knowledge of substances elimination


**pH = 4.5-8**

# Urine sample- post mortem

**High metabolites concentration** → Time gap between consumption and sampling

**Low parent drug concentration in urine & high concentration in blood** → Death happen quickly after consumption

# Hair sample

## Advantages

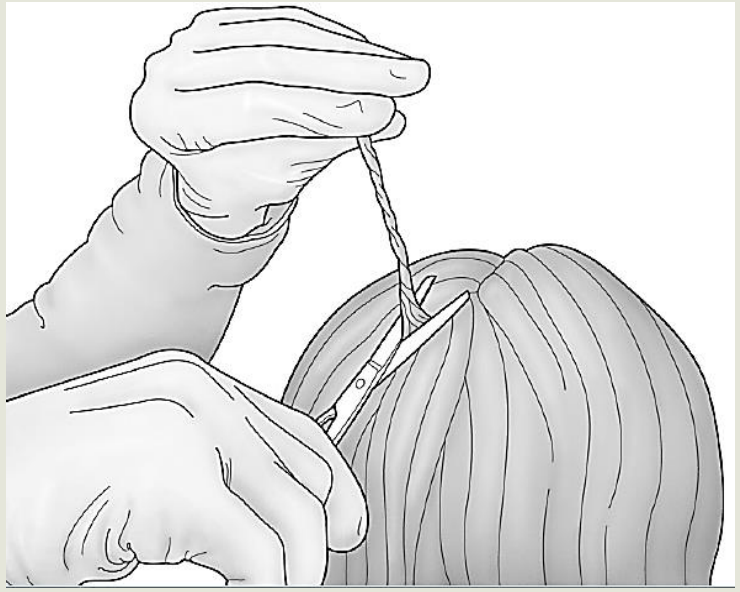
- Available sample. Stored in room temperature
- Can be analysed after years of collection
- Window of detection : weeks to months

used for acute & chronic poisoning , drug usage history

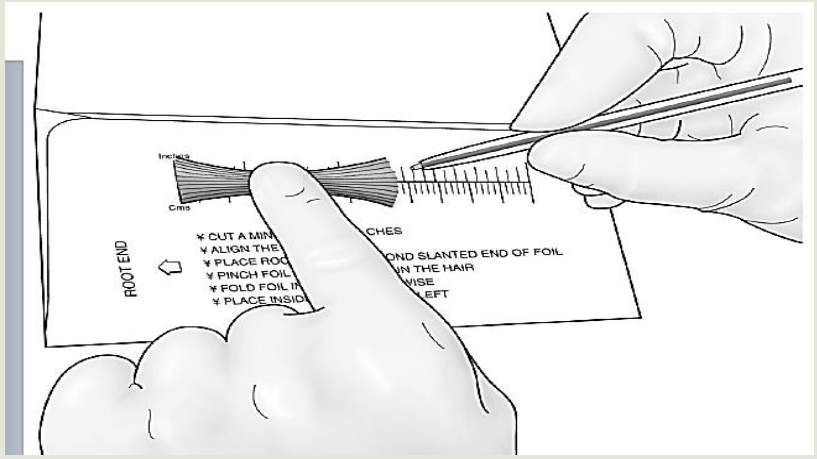
## Disadvantages

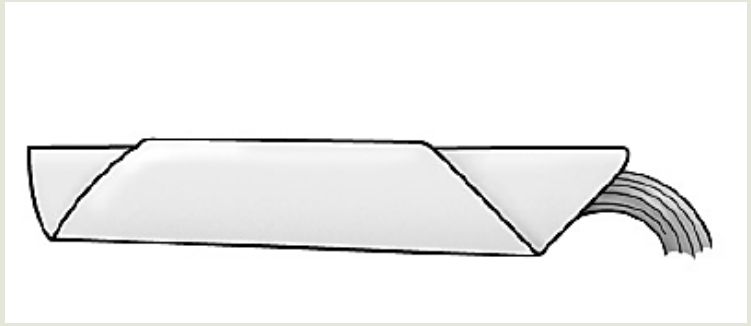
- External contamination
- Large quantities are required for analysis
- Very low concentrations Require sensitive and expensive analytical techniques

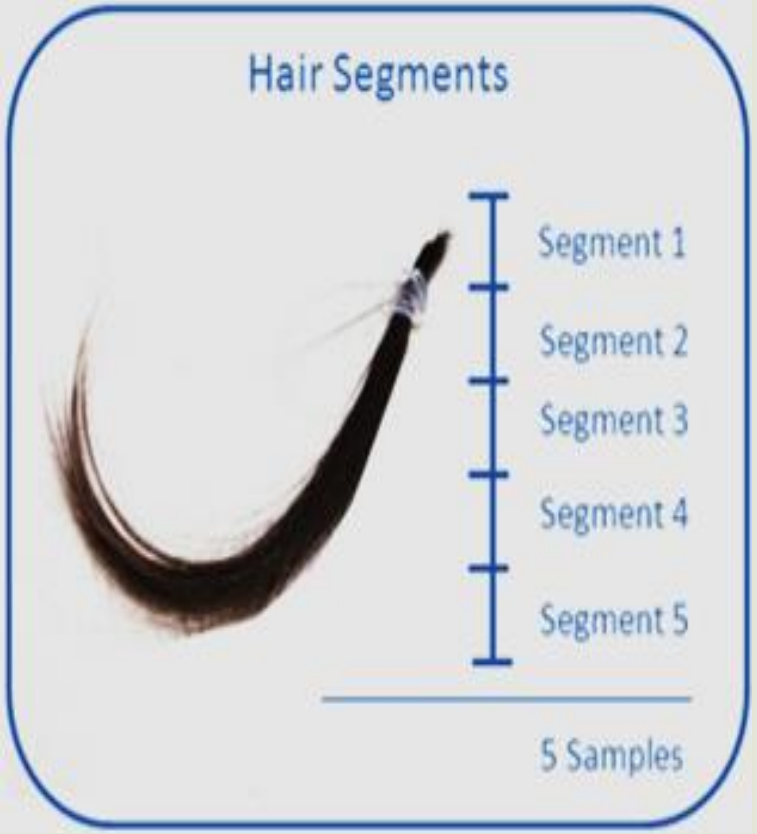
# Hair

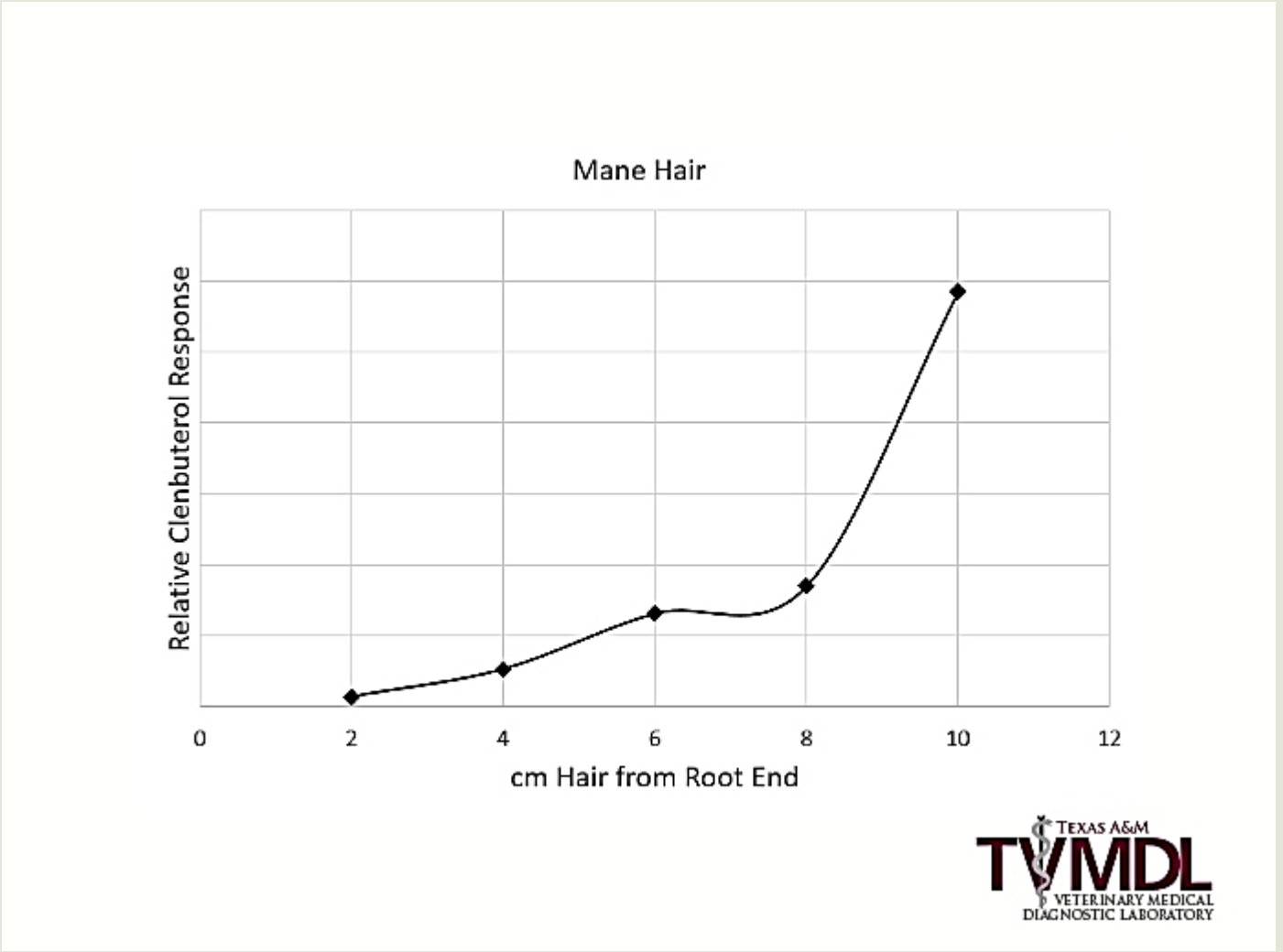


4 weeks after consumption



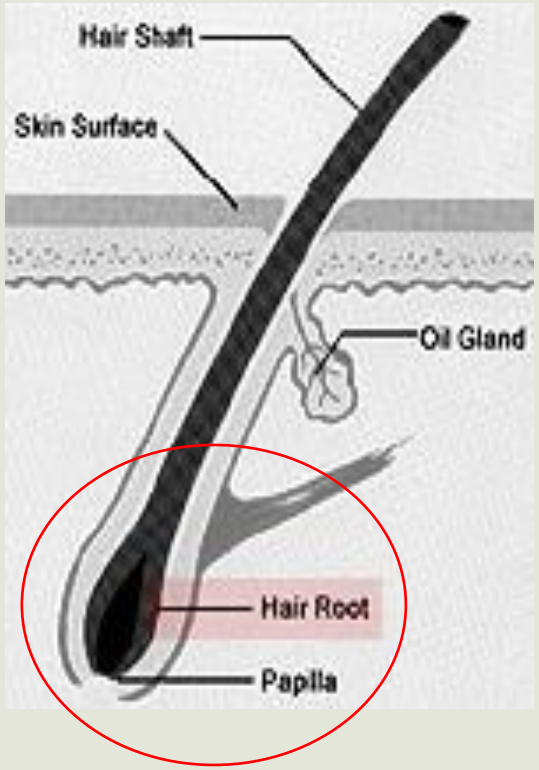

Hair Segments
Segment 1
Segment 2
Segment 3
Segment 4
Segment 5
5 Samples


Mane Hair
Relative Clenbuterol Response
0
2
4
6
8
10
12
cm Hair from Root End
Texas A&M
TVMDL
Veterinary Medical
Diagnostic Laboratory

# Hair sample

**Melanin** | **Lipophilicity** | **Basicity**

- Pubic hair & underarm hair can be analysed
- Beard hair not recommended because of contamination with saliva
- Hair bulb after death
- Parent drug concentration » Metabolites
- **Examples of drugs** : heroin, cocaine, benzodiazepines, amphetamine & derivatives , heavy metals



# Nail Sample

- When hair is not available
- 100 -150 mg. Storage at room temperature
- **Advantage** :
  Drug concentrations remain relatively constant for prolonged periods
  Can be used in post-mortem cases
- **Examples**: Arsenic / cannabinoids / opiates / cocaine/ phencyclidine / benzodiazepines / methadone
- Fingernails grow at 3 mm/month and toenails grow at 1 mm/month
- The rate of growth may be influenced by age, cold, and malnutrition

# Nail Sample

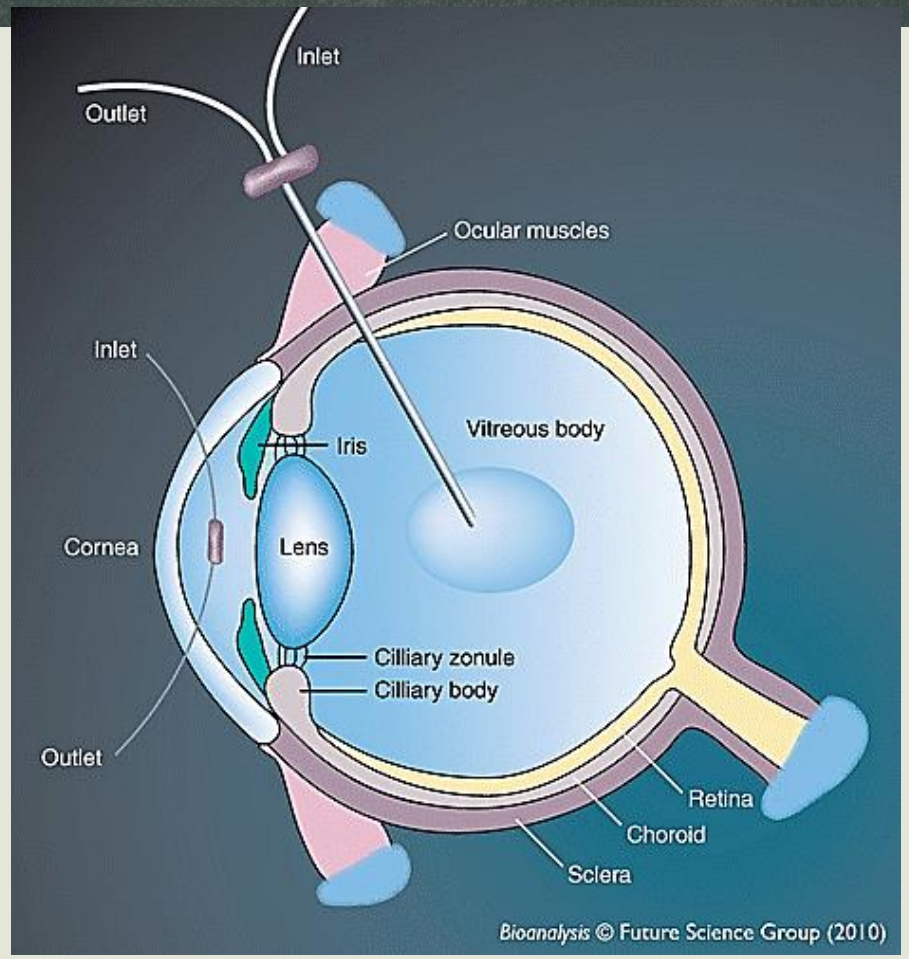
- **Mee Lines**
  - White lines of discoloration across the nails
  - Results from illness or poisoning
  - Poisoning with : Arsenic / Thallium / carbon monoxide

- **Azure Lunula**
  - It is called Argyria
  - Silver poisoning / Wilson’s disease / Raynaud's disease

# Vitreous humour

## Advantages

- Sterile & isolated compartment
- No post-mortem redistribution
- Longer time for petrification to occur
- Existence of peripheral compartment: slow absorption & slow elimination
- Mostly free drugs (unbounded)




## Disadvantages

- Low volume (2-3 ml)

# Vitreous humour

**Ethanol**

Is not produced by fermentation after death

**Heroin**

Detection of 6 monoacetylmorphine / metabolite of heroin

Does not contain hydrolase

- Digoxin , salicylate , aspirin
- glucose, urea, nitrogen, uric acid, creatinine, sodium and chloride
- Studies : concentrations in V.H is proportional to blood concentrations 1-2 hours before death
- Sodium fluoride is added in clinical tests, not in forensic tests

# Saliva / Oral fluid Sample

## Advantages

- Available sample. Not easy to be manipulated
- Window of detection is similar to blood
- Work place drug testing , traffic accidents

**pH = 5.6-7.9**

- Concentration of acidic drugs are lower than blood
- Concentration of Basic drugs are more than blood
- **Examples**: Ethanol, opioids , cocaine, methadone

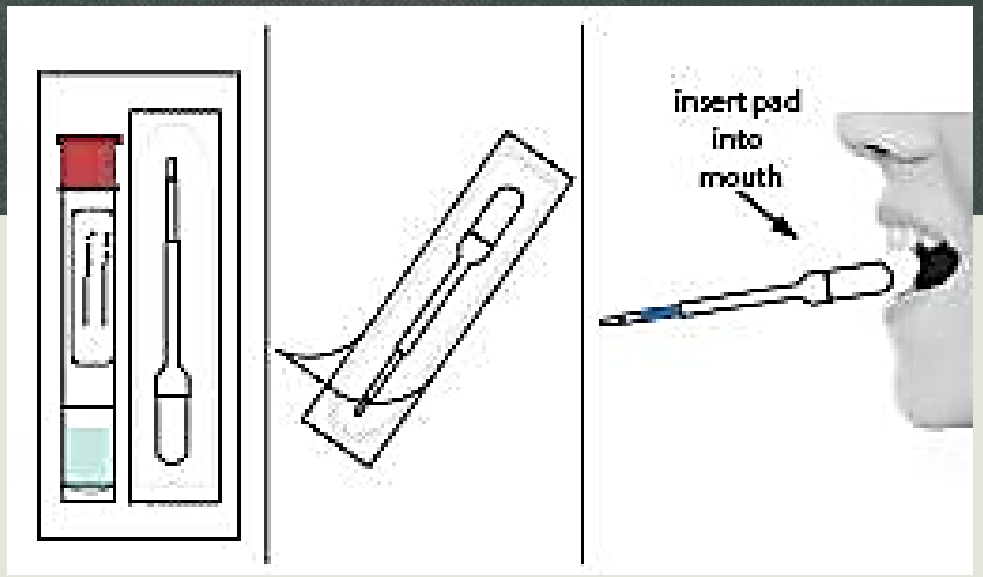
# Saliva / Oral fluid Sample

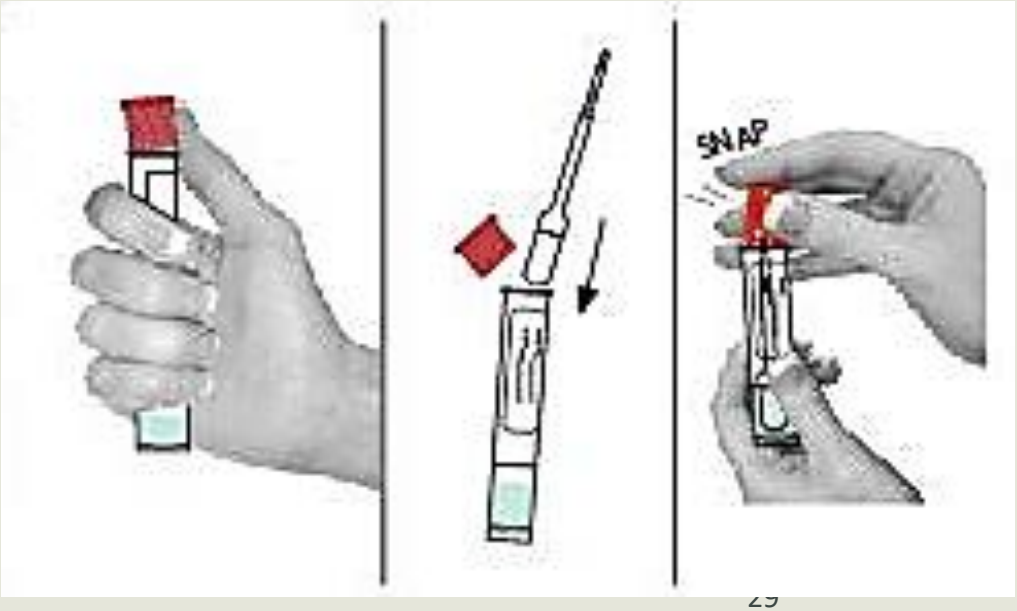
## Disadvantages

- Short window of detection
- Need to induce secretion

  Induction of secretion can change pH, therefore change drug concentrations

- Collection device can affect drug concentrations



# Sweat sample

## Advantages

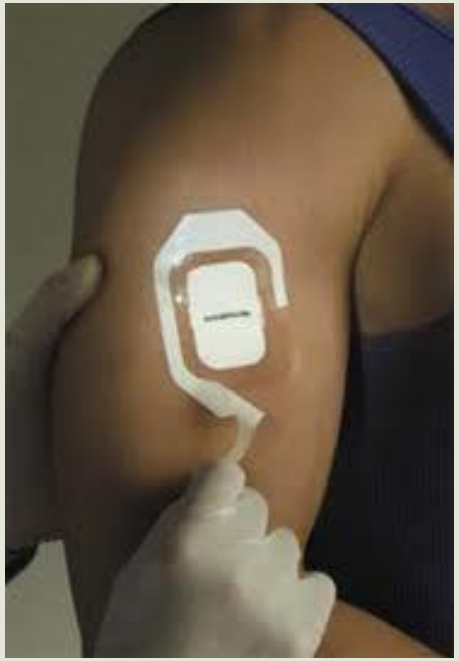
- Routine tests for more than 14 days
- Cheap cost
- Long window of detection

## Disadvantages

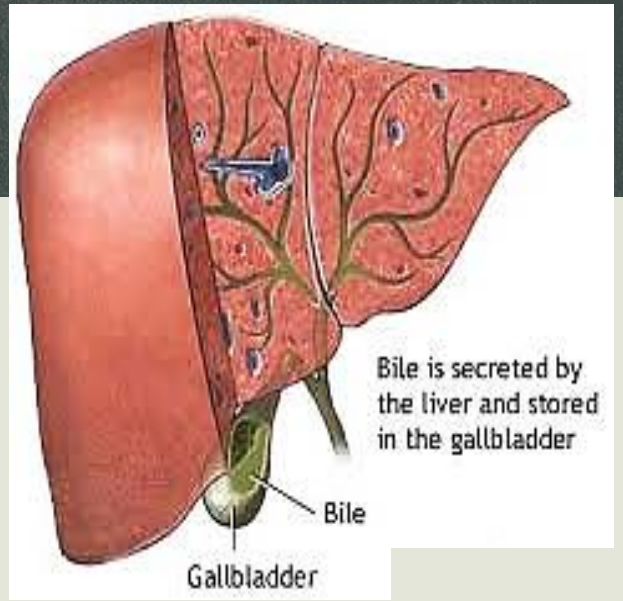
- Low concentration
- External contamination

➢ **Examples of drugs**: Cocaine & codeine

**Sweat Patches**



# Bile sample



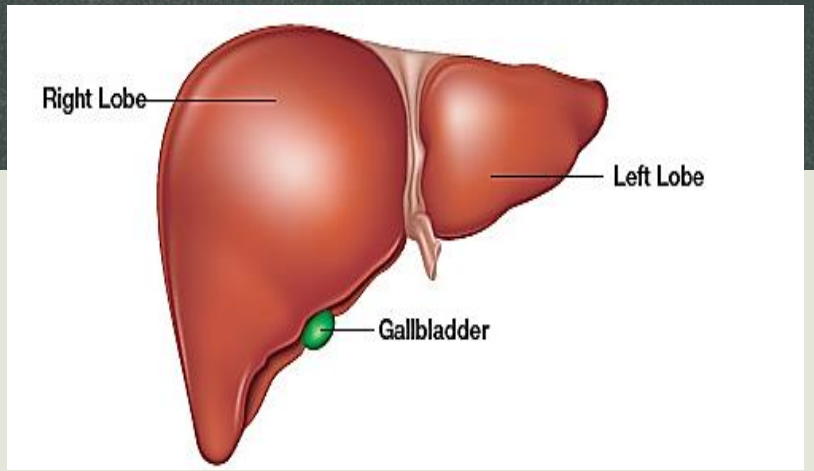

- Collected prior to liver sample to avoid contamination\
- Chronic drug use history
- Concentrations in bile is more than blood
- **Examples of drugs** : Alcohol. Bounded drugs like opioids (morphine) and benzodiazepines.

**15 ml**

## Disadvantages

- Difficulty in extraction because of bile salts & lipids

# Liver sample




## Advantages

- Large sample. Easy to be collected and analysed
- Lots of reference data available
- Right lobe is less susceptible for post-mortem redistribution in blood

## Disadvantages

- High lipid content: quick to undergo petrification
- Contaminated with gastric contents


**TCA concentrations are higher in liver than in blood**

# Gastric contents

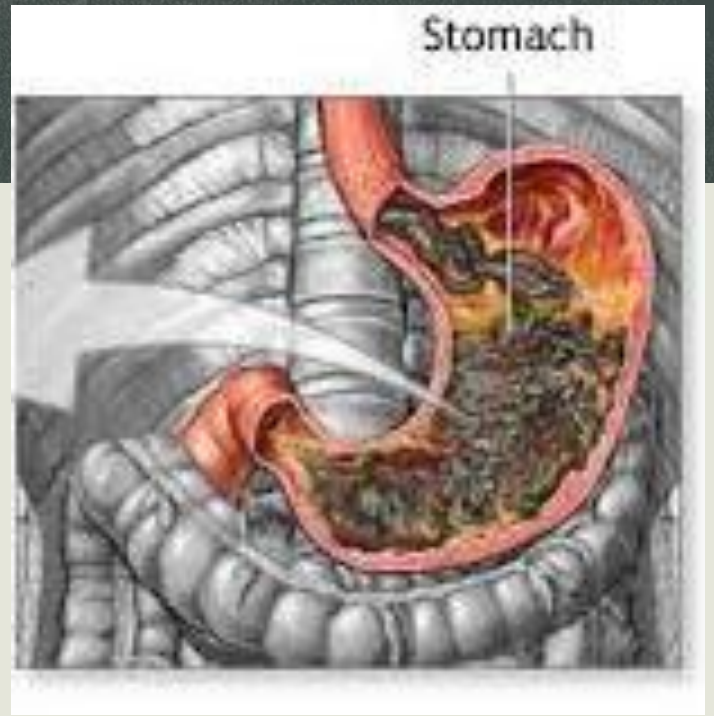

## Advantages

- High concentration short time after consumption
- Not affected by metabolism
- Specific odour or instrument can indicate the poison

## Disadvantages

- Not homogenous . Analyse all volume
- Can be contaminated by bile

# Gastric contents




- Stomach content, vomiting

- Odour can indicate the poison
  Garlic odour : arsenic , phosphine
  Shoe polish : nitrobenzene

- Very careful in case of cyanide or aluminium phosphide , because of toxic gas

# Gastric contents

**Notes**

- High concentration of parent drug → Oral consumption
- Parent drug cannot be detected → Does not exclude oral consumption
- Detection of metabolites / or morphine in high quantities → Transport from blood (especially basic compounds, because of ion trapping)

  Not necessary oral consumption

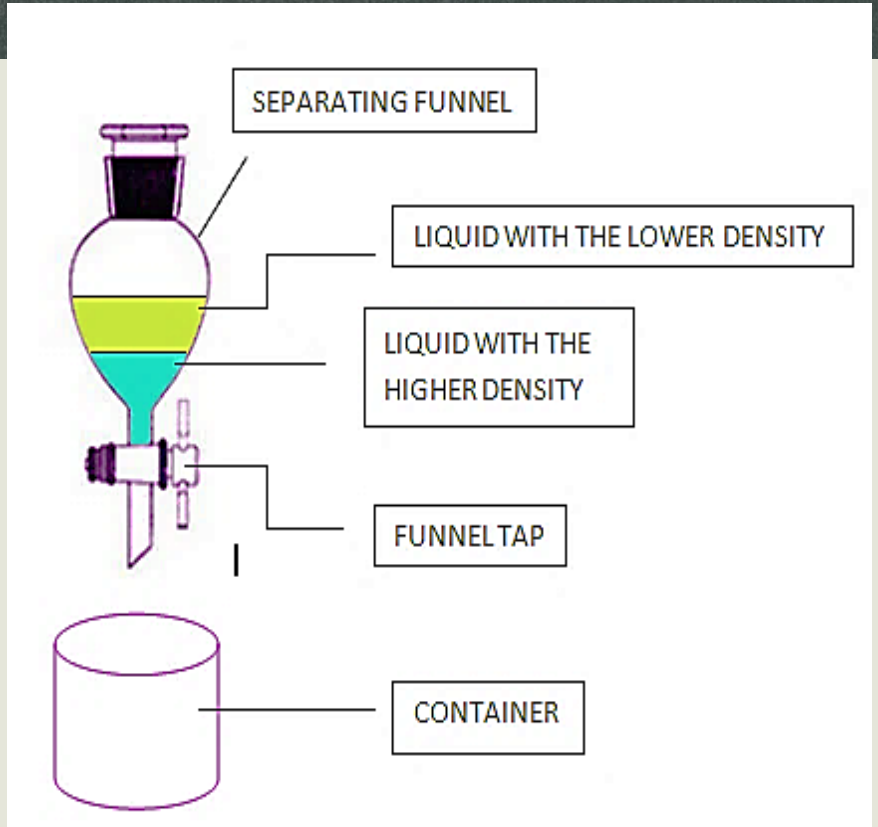
# Meconium

- 1-4 days after birth / black to green stool
- Foetus exposure to drugs
- Window of detection : 20 weeks prior to birth
- Complicated & inhomogeneous sample
- Difference between foetus, infant and adult metabolism
- Examples: cocaine usage by the mother / ethanol

# Preparing samples for analysis

## Liquid-liquid extraction

- **Organic solvent**: good extraction / lower density than water / low solubility in water/ inert / low toxicity and nonflammable / inexpensive and available
- pH is adjusted to convert drug into non-ionic form in order to be transferred to organic phase (usually pH is adjusted two units above or below pKa)




Ethyl acetate , Acetonitrile, dichloromethane, Hexane , toluene, diethyl ether, chlorobutane, , chloroform

# Preparing samples for analysis

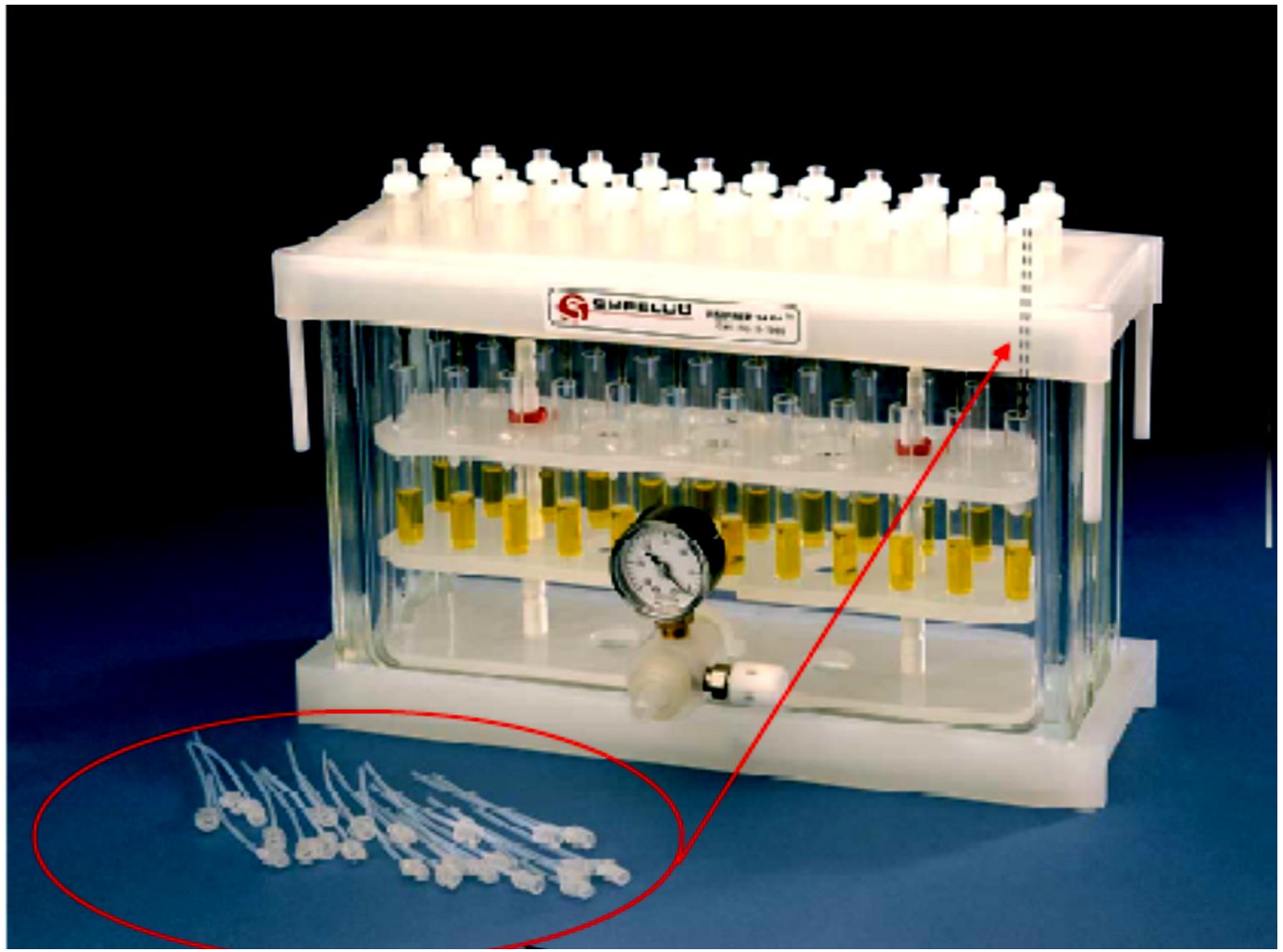
## Liquid-liquid extraction

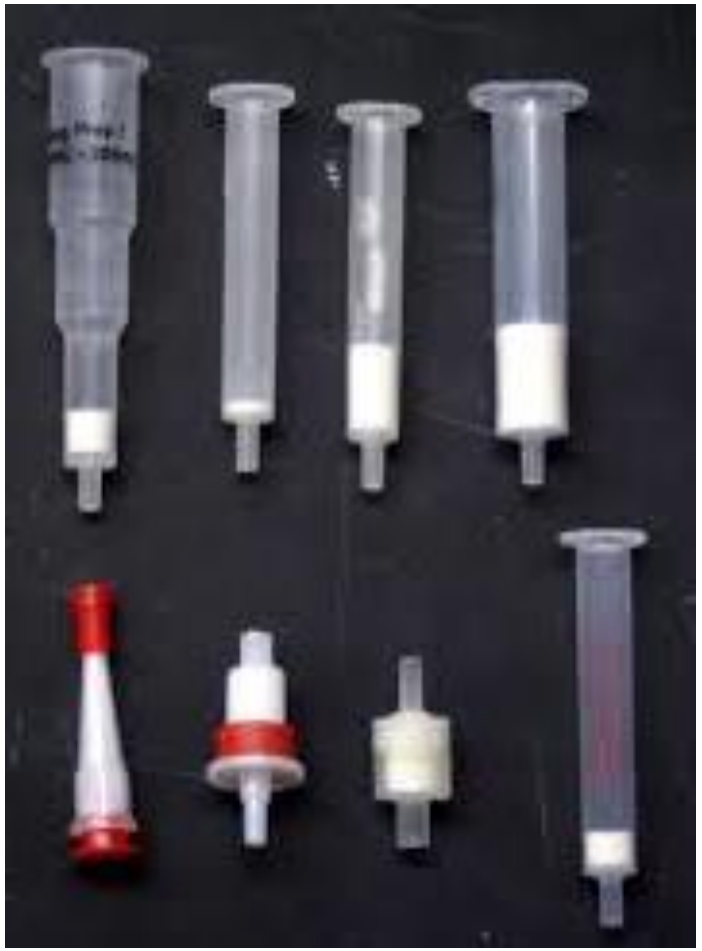
- Use less polar solvents (such as hydrocarbons) to prevent extraction of other substances
- Extraction increases by mixing organic solvents
- To extract strong acidic or basic substances, back extraction can be applied

**Basic substance** → (Add $H_2SO_4$) → Transfer to aqueous phase → (Add NaOH) → Transfer to organic phase

# Preparing samples for analysis

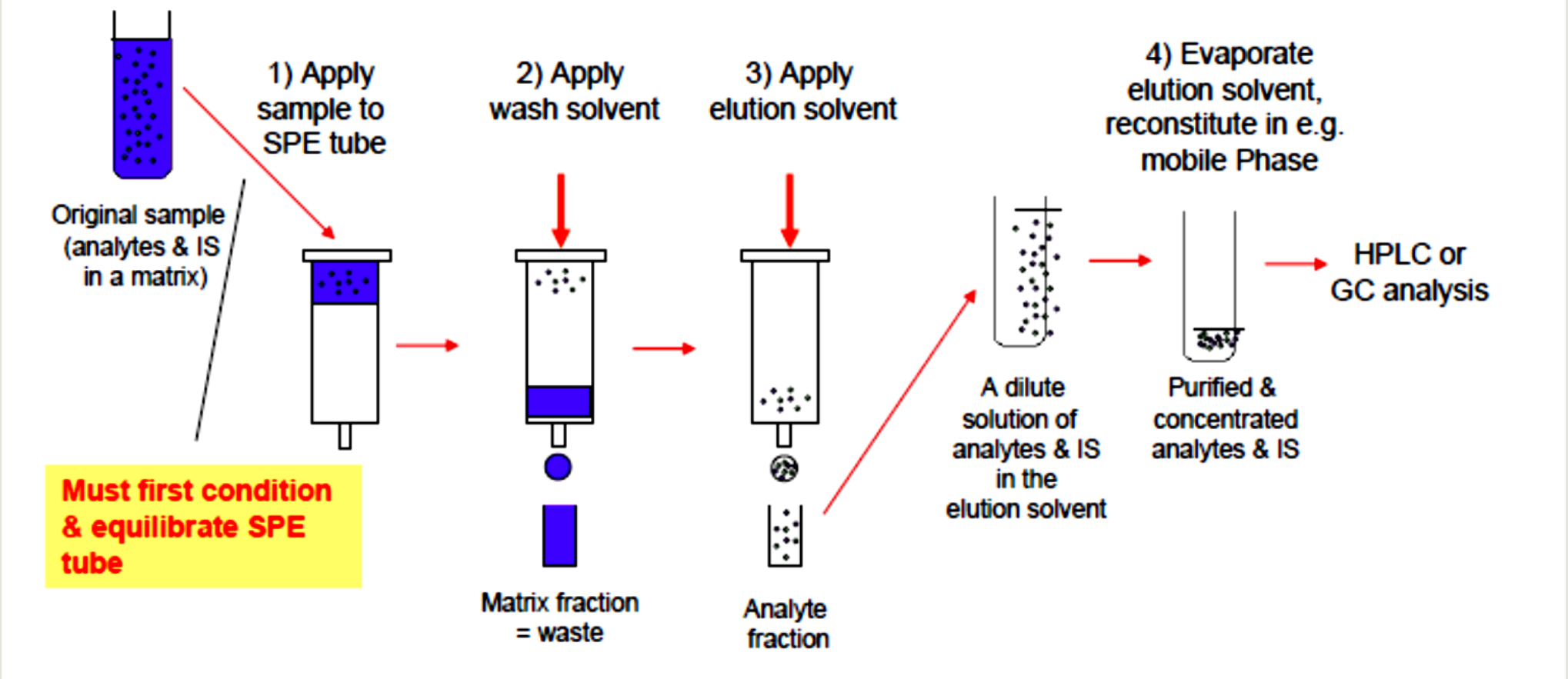
## Solid phase extraction (SPE)



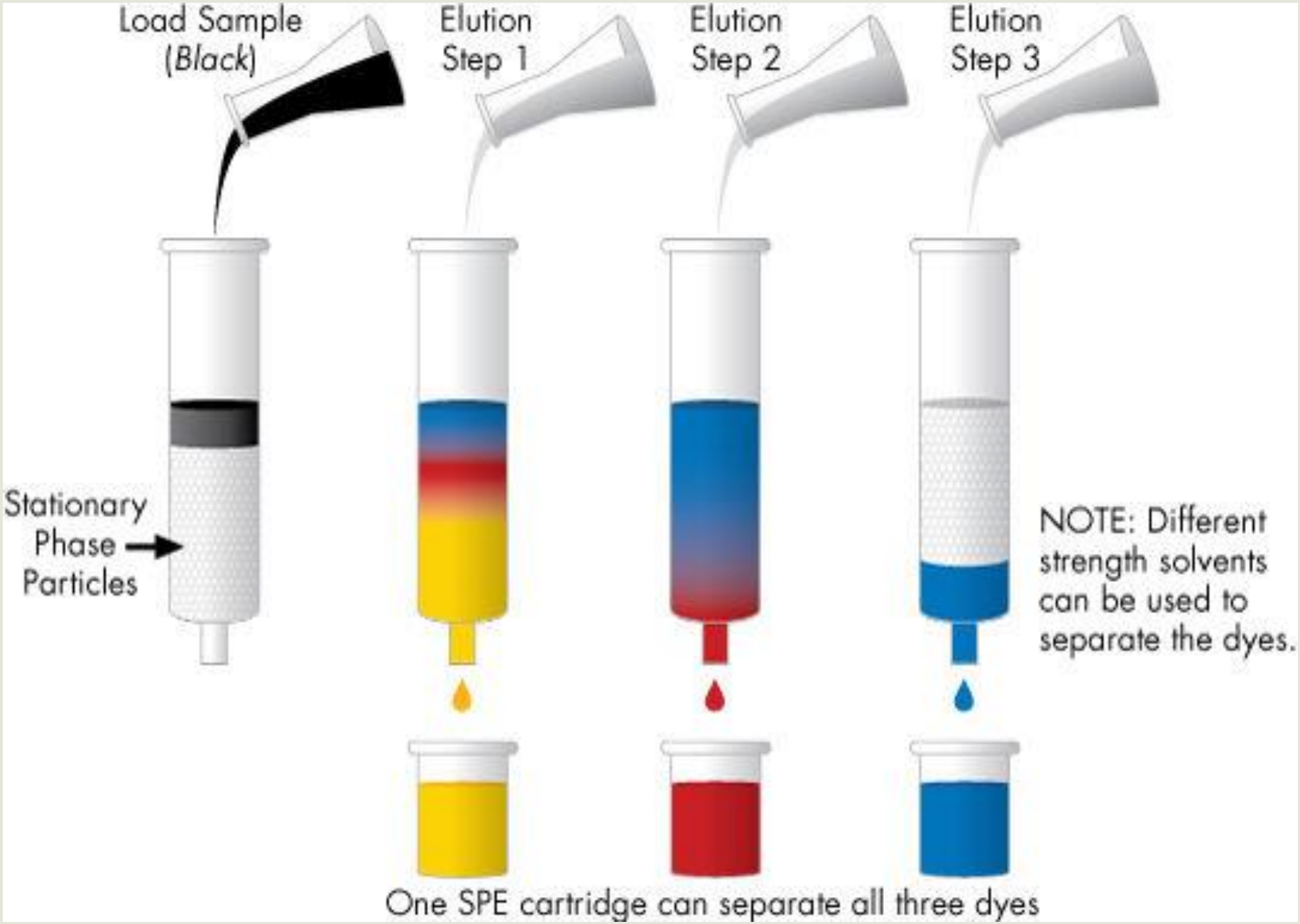


**Column liquid-solid chromatography**

# Solid phase extraction (SPE)



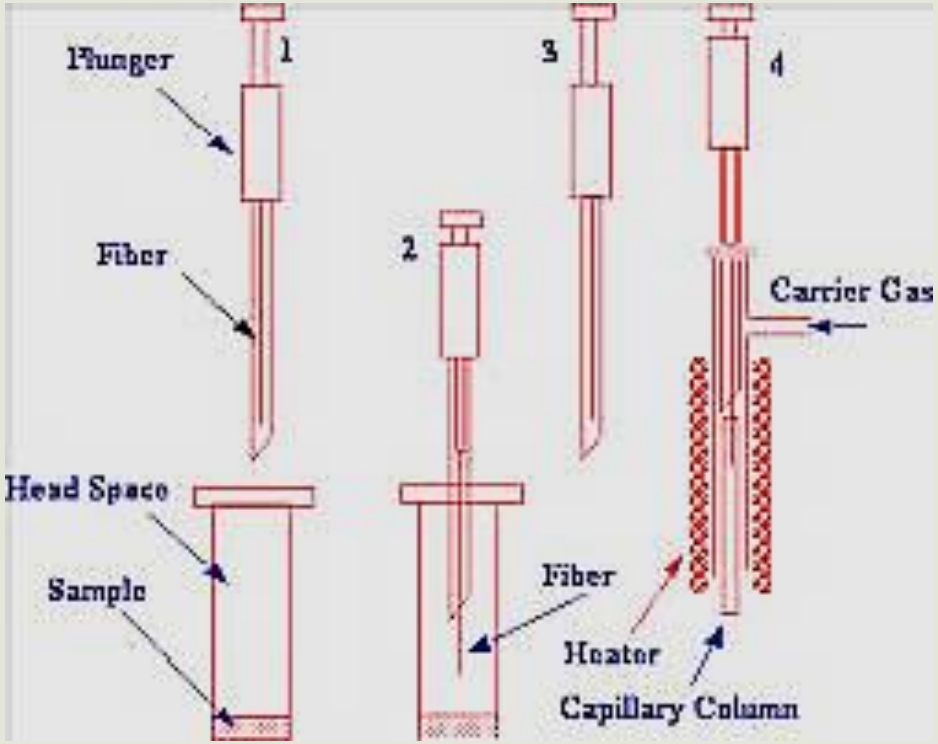

**Advantages**: High selectivity , great separation and recovery , short analysis time, Low solvent volumes, automation

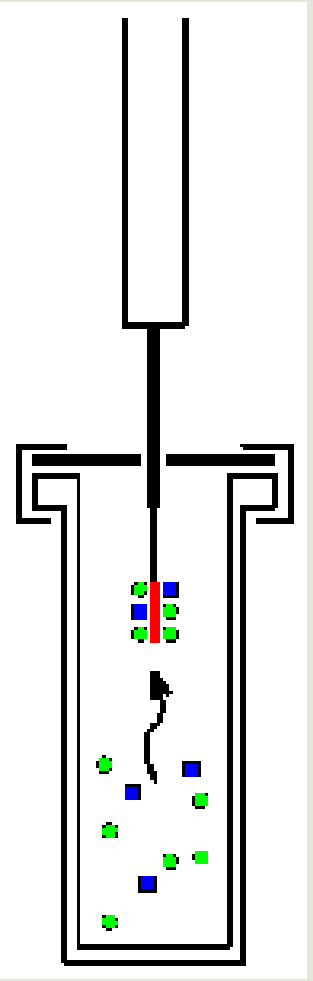

Load Sample
(Black)
Elution
Step 1
Elution
Step 2
Elution
Step 3
Stationary
Phase
Particles
NOTE: Different
strength solvents
can be used to
separate the dyes.
One SPE cartridge can separate all three dyes

# Preparing samples for analysis

## Solid phase micro  extraction (SPME)

- The use of a coated fibre to extract analytes
- **Advantages:** simple, quick , no solvents needed , One step analysis, compatible with gas chromatography or HPLC



# Screening methods

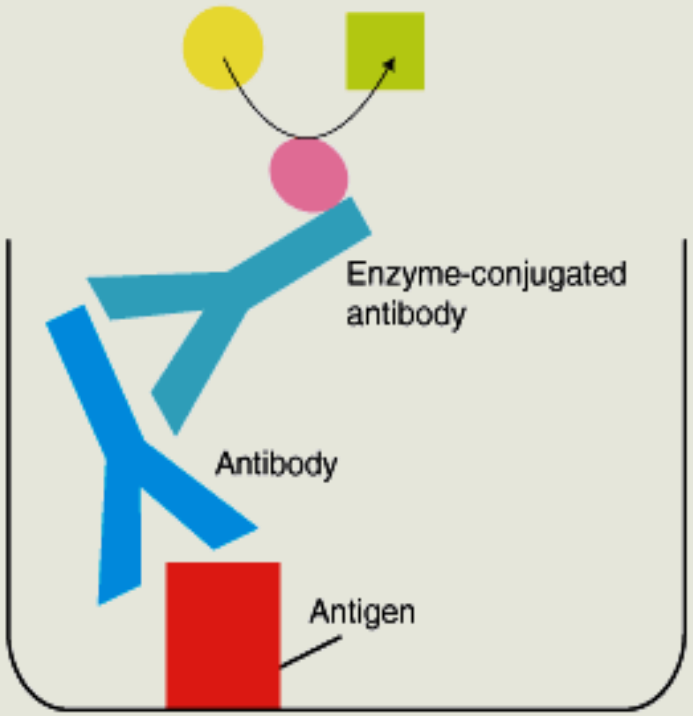
**ELISA**

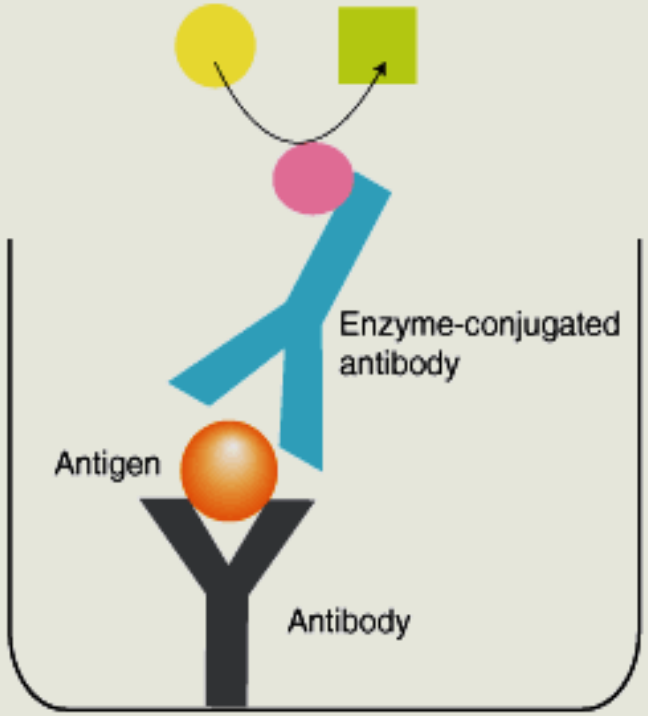
- **Antibodies**

**TLC**

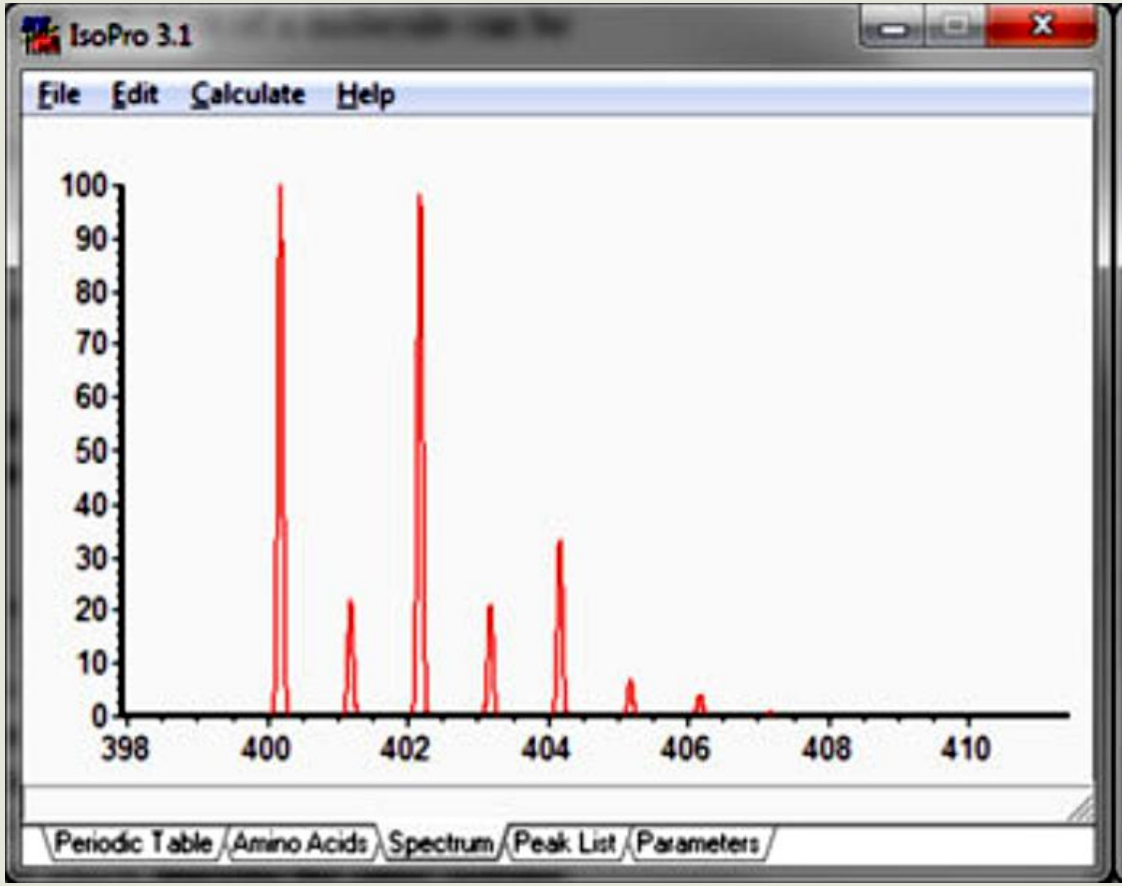
- **RF**

**Colour tests**




- **Marquis Test :** for amphetamines and opioids
  Solution of concentrated $H_2SO_4$ + formaldehyde

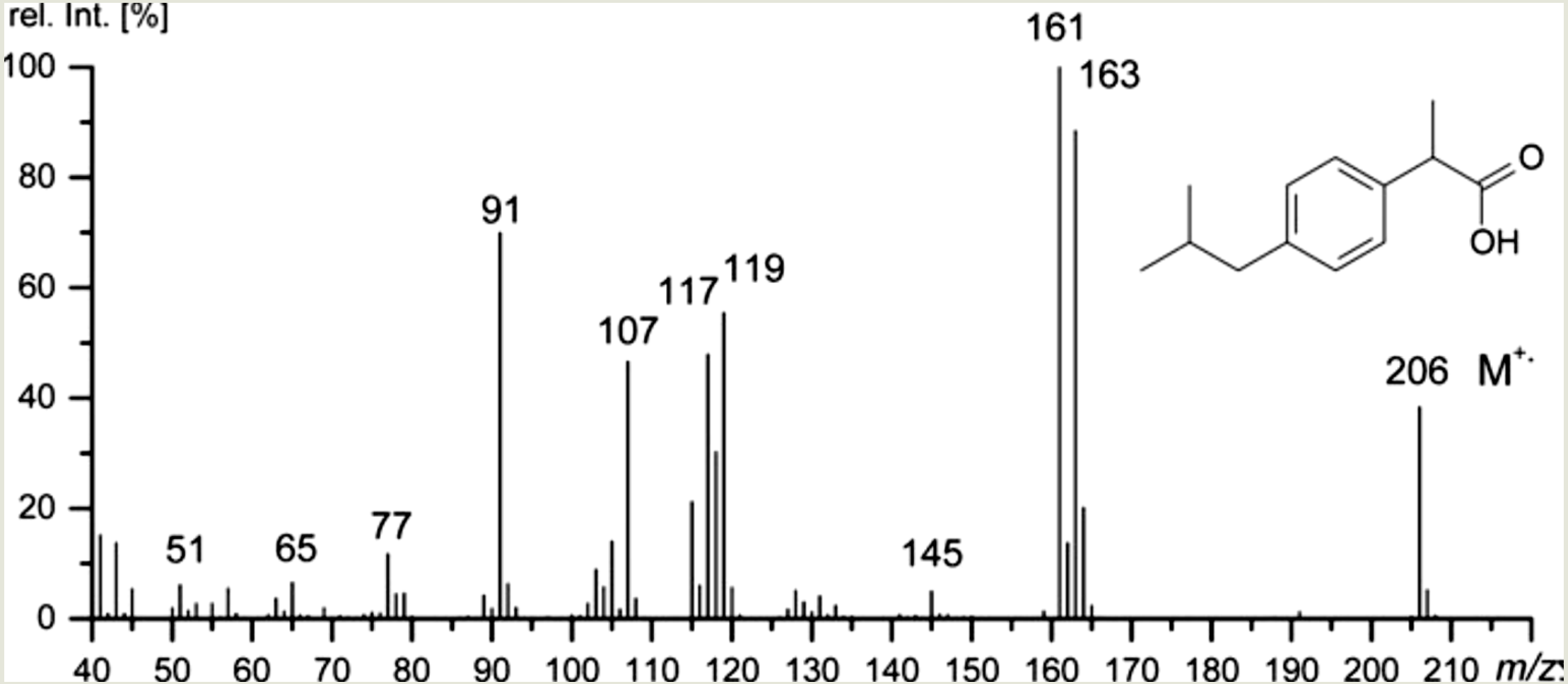



IsoPro 3.1

File Edit Calculate Help

| m/z | Abundance | Spread | Multiplicity |
|---|---|---|---|
| 401.84471 | 0.999911 | 8.99851 | 52 |
| 400.17024 | 0.3490230 | 0.00000 | 1 |
| 401.17367 | 0.0758697 | 0.00282 | 3 |
| 402.16667 | 0.3440645 | 0.01339 | 5 |
| 403.16993 | 0.0735987 | 0.01337 | 8 |
| 404.16334 | 0.1159608 | 0.02393 | 7 |
| 405.16629 | 0.0240557 | 0.01336 | 8 |
| 406.16078 | 0.0142757 | 0.02392 | 7 |
| 407.16301 | 0.0027287 | 0.01336 | 7 |
| 408.16539 | 0.0003090 | 0.01054 | 4 |
| 409.16781 | 0.0000249 | 0.00245 | 2 |

Periodic Table Amino Acids Spectrum Peak List Parameters


rel. Int. [%]
100
80
60
40
20
0
161
163
91
107
117
119
206
M+·
51
65
77
145
O
OH
40
50
60
70
80
90
100
110
120
130
140
150
160
170
180
190
200
210
m/z

# In Court

- In courts, acceptable methods are chromatography (LC/MS , GC/MS, HPLC) and tandem MS/MS for very low concentrations

- Calibration curve , usage of a blank , made duplicate or triplicate of the same sample and take the mean ± SD , use internal and external standards

- **Method validation**

| | | |
|---|---|---|
| **Linearity** | **LOD and LOQ** | **Recovery** |
| **Selectivity** | **Accuracy** | **Precision** |

- Test the instrument periodically

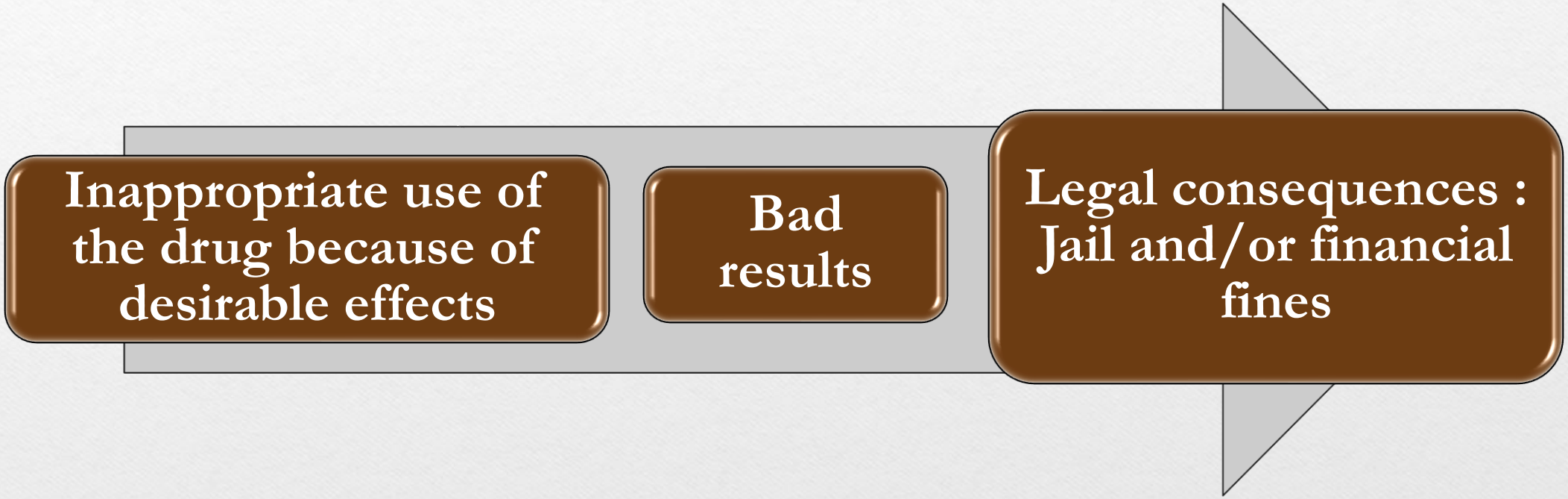
# Forensic Toxicology

## Drugs of Abuse –1–



Dr Samar Alzeer

# Drugs of Abuse



# Drugs of Abuse Classifications

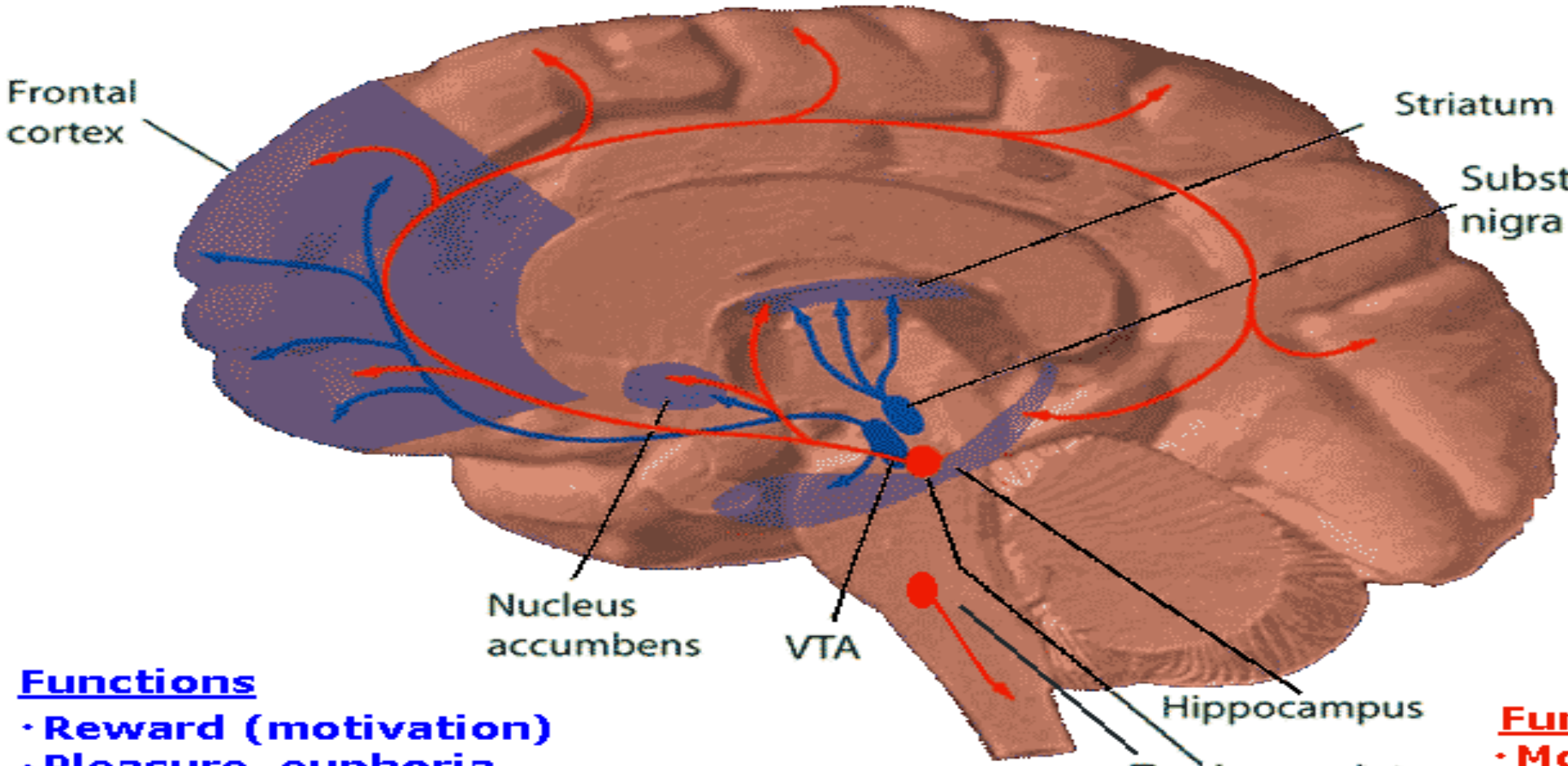
| USA | Description |
|---|---|
| **Schedule I** | Drugs with no currently accepted medical use and a high potential for abuse |
| **Schedule II** | Drugs with a high potential for abuse, with use potentially leading to severe psychological or physical dependence |
| **Schedule III** | Drugs with a moderate to low potential for physical and psychological dependence |
| **Schedule IV** | Drugs with a low potential for abuse and low risk of dependence |
| **Schedule V** | Drugs with lower potential for abuse than Schedule IV :preparations containing limited quantities of certain narcotics |

# Drugs of Abuse

| UK |
| --- |
| Class A |
| Class B |
| Class C |
| Temporary class drugs |

## Dopamine Pathways

## Serotonin Pathways



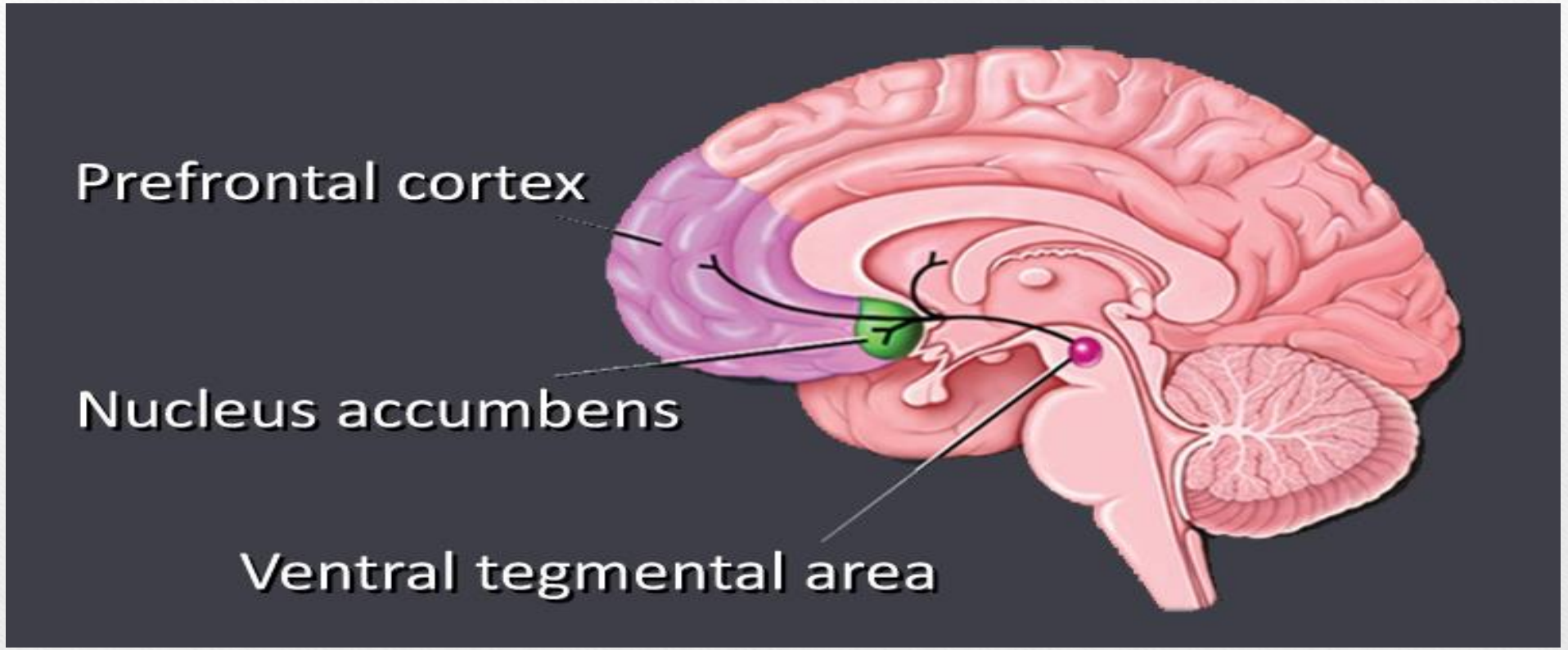

**Functions**

- Reward (motivation)
- Pleasure, euphoria
- Motor function (fine tuning)
- Compulsion
- Perseveration

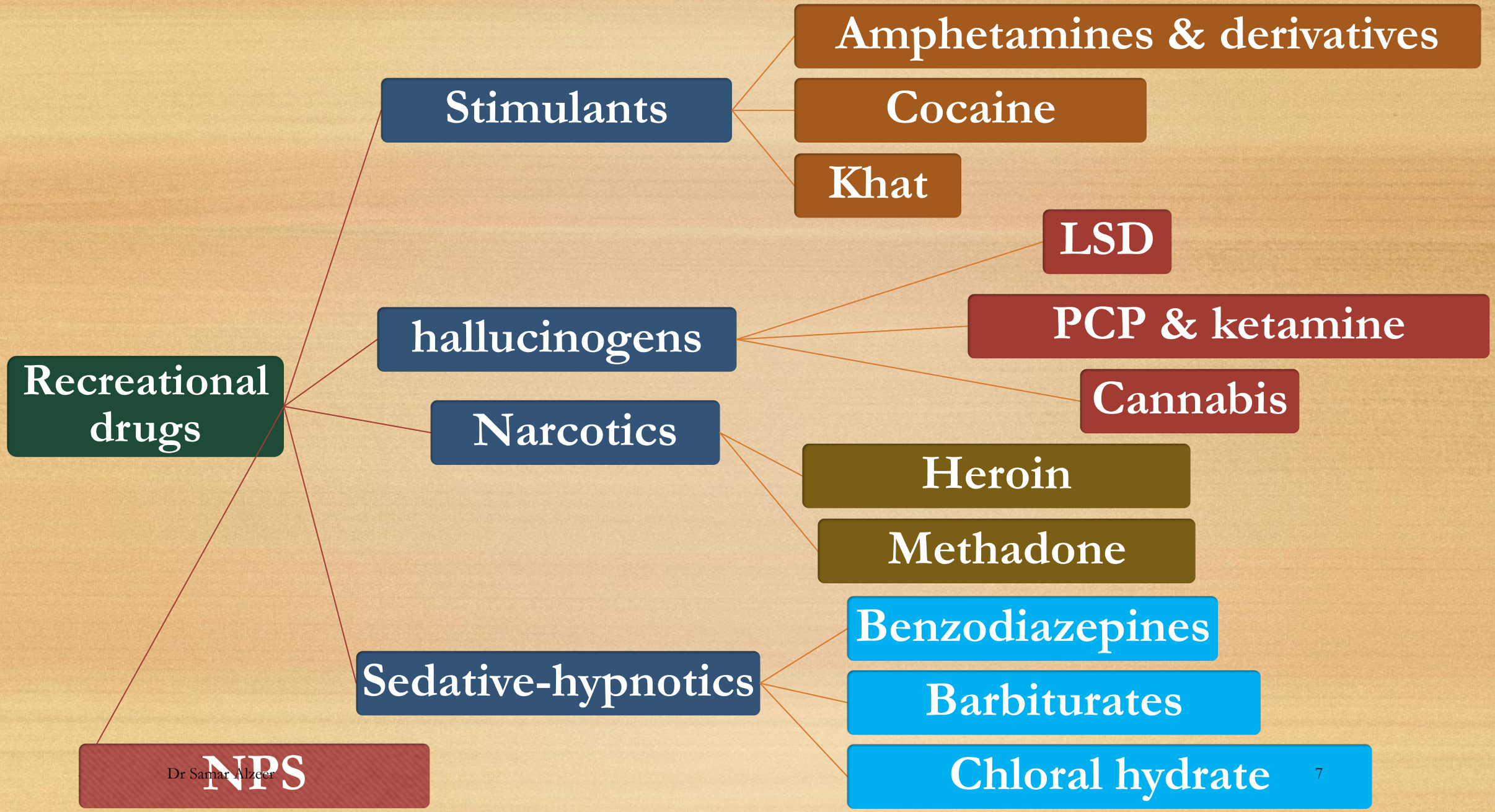
**Functions**

- Mood
- Memory processing
- Sleep
- Cognition

# The Reward Pathway




## Dopamine & Addiction


Recreational drugs
Stimulants
Amphetamines & derivatives
Cocaine
Khat
hallucinogens
LSD
PCP & ketamine
Cannabis
Narcotics
Heroin
Methadone
Sedative-hypnotics
Benzodiazepines
Barbiturates
Chloral hydrate
NPS

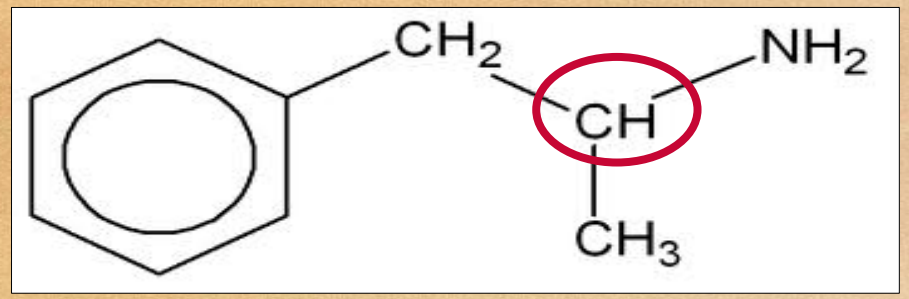
# Stimulants

- Amphetamine derivatives
- Cathinone
- Cocaine

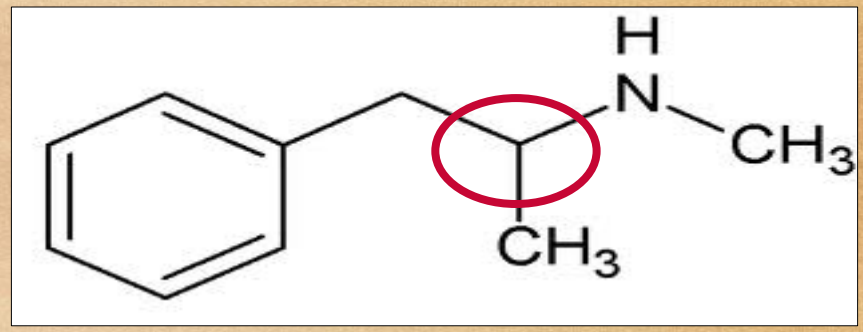

# Physiological Changes During *Fight or Flight* Response

- Breathing Rate
- Heart Rate
- Blood Pressure
- Muscle Tension
- Stress Hormones
  - Epinephrine
  - Norepinephrine
  - Cortisol

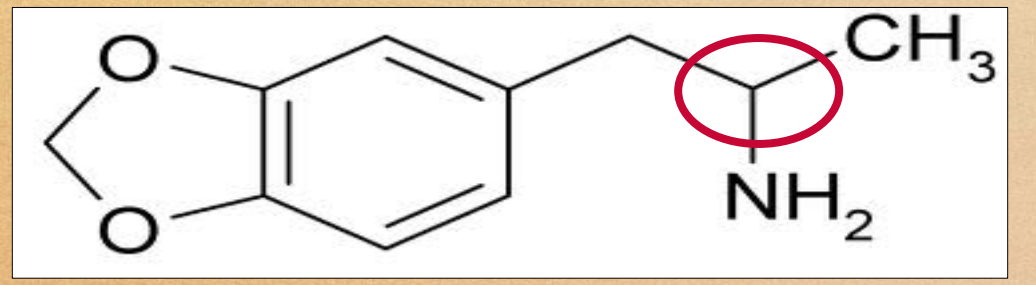
# Amphetamines & derivatives



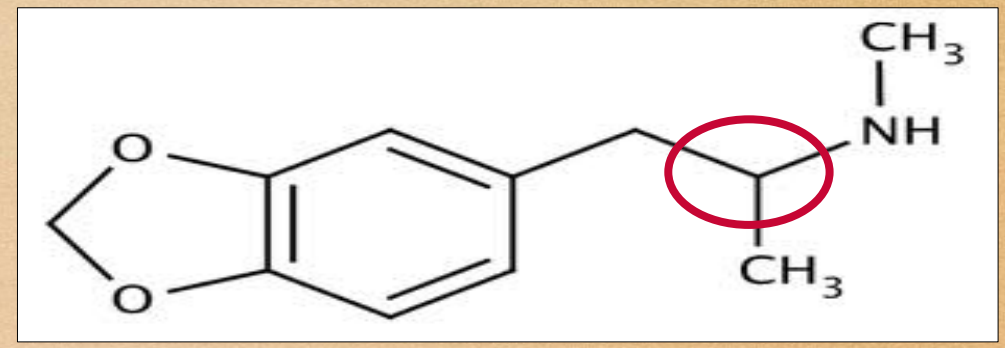

Amphetamine




Methamphetamine (Meth)

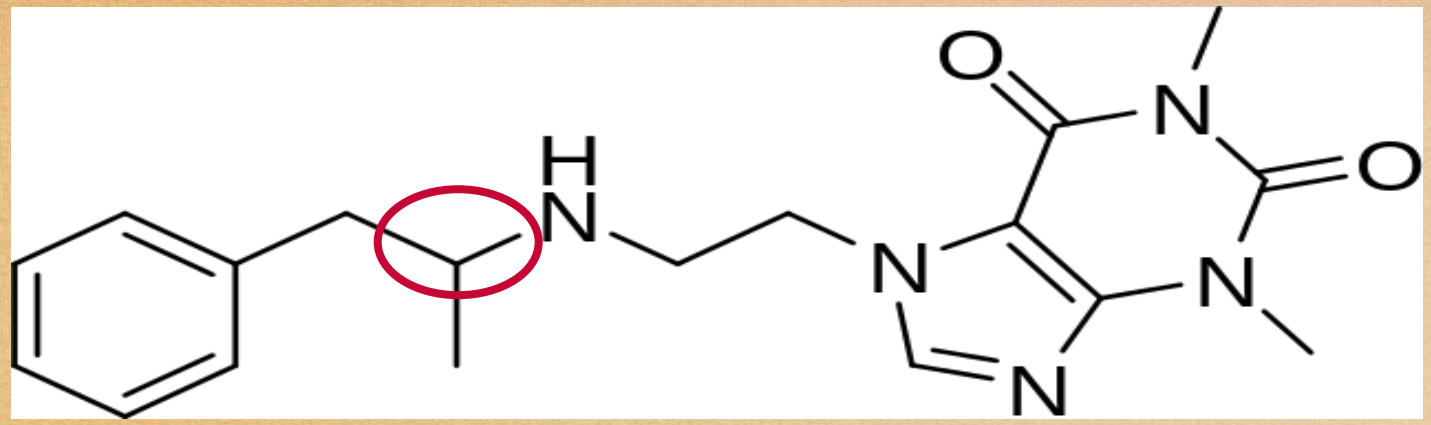



3,4 Methylenedioxy amphetamine (MDA)




3,4 Methylenedioxy methamphetamine (MDMA) (Ecstasy)

# Amphetamines & derivatives




Captagon (Fenethylline)

# Amphetamines & derivatives

| Types |
| --- |
| Tablet |
| Nasal spray |
| Smoking |
| i.v. injection |

| Drug | USA | UK |
| --- | --- | --- |
| **Amphetamine** | Schedule II | Class B |
| **Methamphetamine** | Schedule II | Class A |
| **MDMA** | Schedule I | Class A |
| **Fenethylline** | Schedule I | Class C |

# Amphetamines & derivatives

| Medical uses |
| --- |
| Treatment of obesity |
| Antidepressant |
| Sleep disorders |
| Nasal congestion |
| Attention Deficit Hyperactivity Disorder (ADHD) methylphenidate |

# Amphetamines & derivatives

| Desirable uses |
| --- |
| ➢ Increase physical & mental energy |
| ➢ Increase Endurance |
| ➢ Activation of mind, ecstasy |
| ➢ Increase of alertness & concentration |
| ➢ Increase Self confidence |

| Adverse effects |
| --- |
| Insomnia |
| Depression |
| Nervy |
| Addiction |
| Affect memory at long-term uses |
| Hypertension |
| hyperthermia |

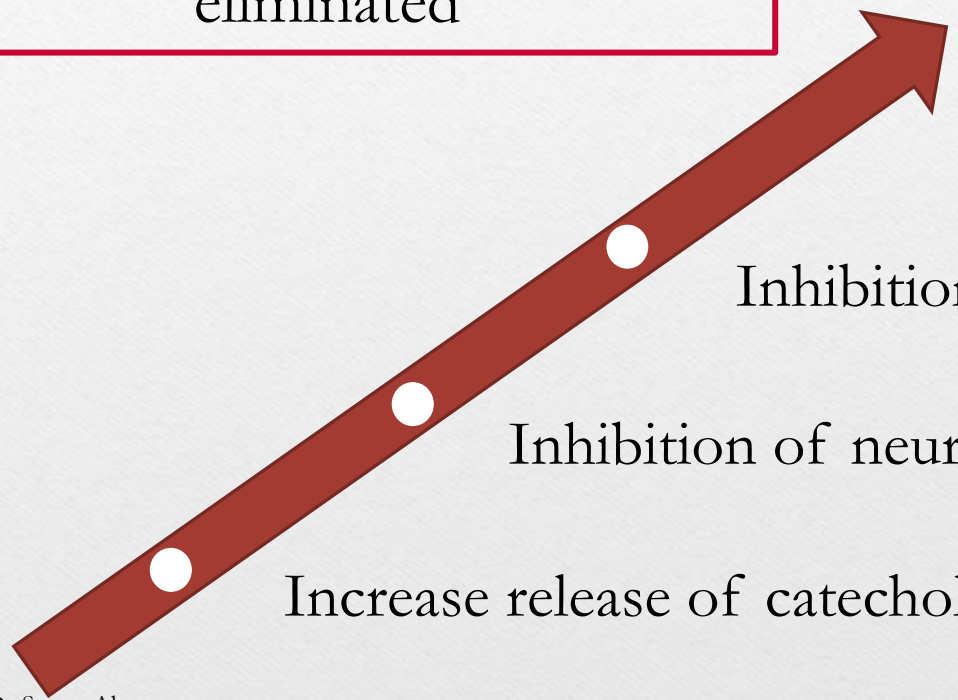
# Mechanism of Toxicity

Amphetamine: D & L isomer
D is more potent & quickly eliminated

**Dopamine** — Meth

**Serotonin** — MDMA

**Noradrenaline**

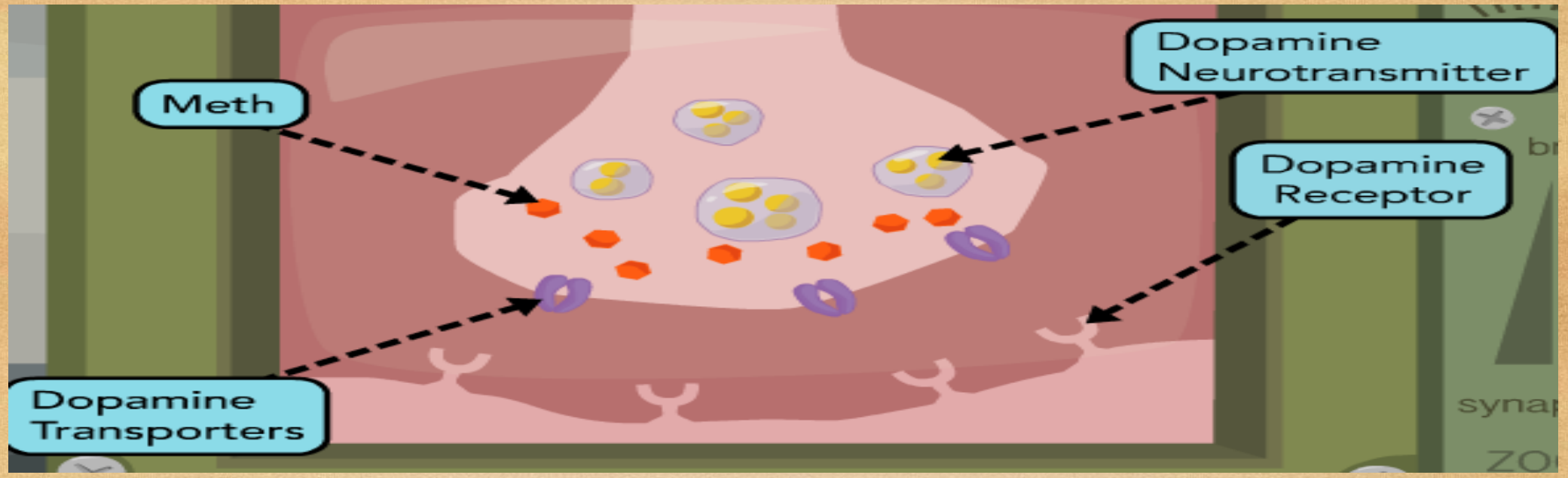


Inhibition of MAO

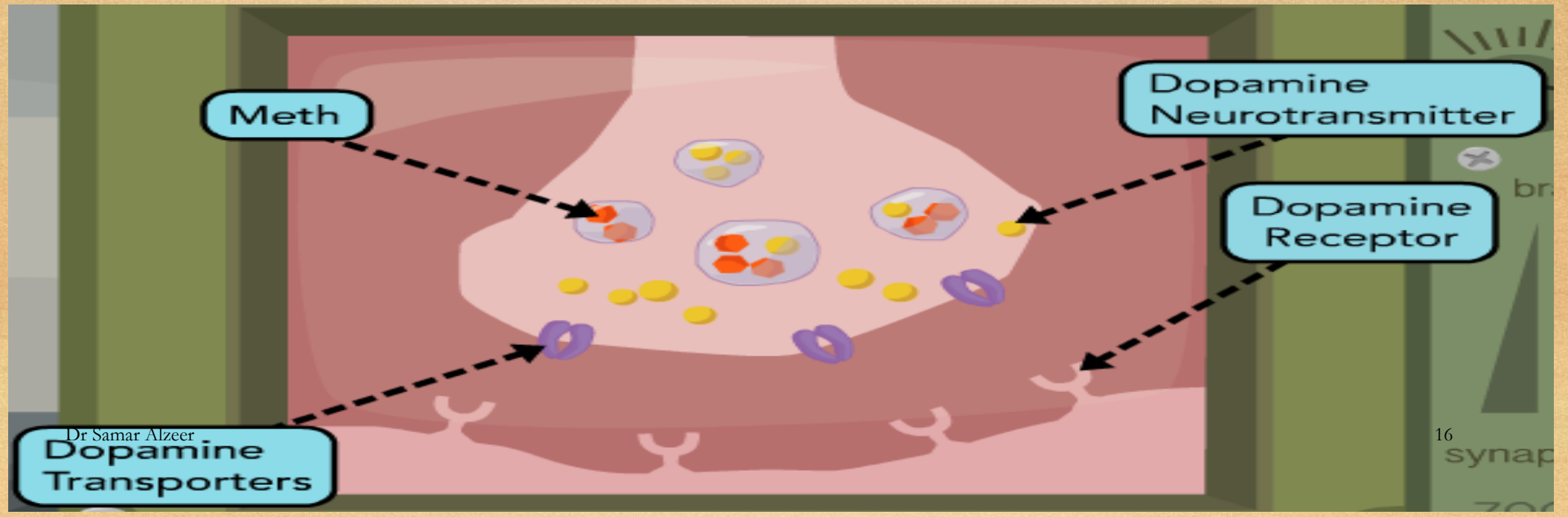
Inhibition of neurotransmitters recapturing

Increase release of catecholamines

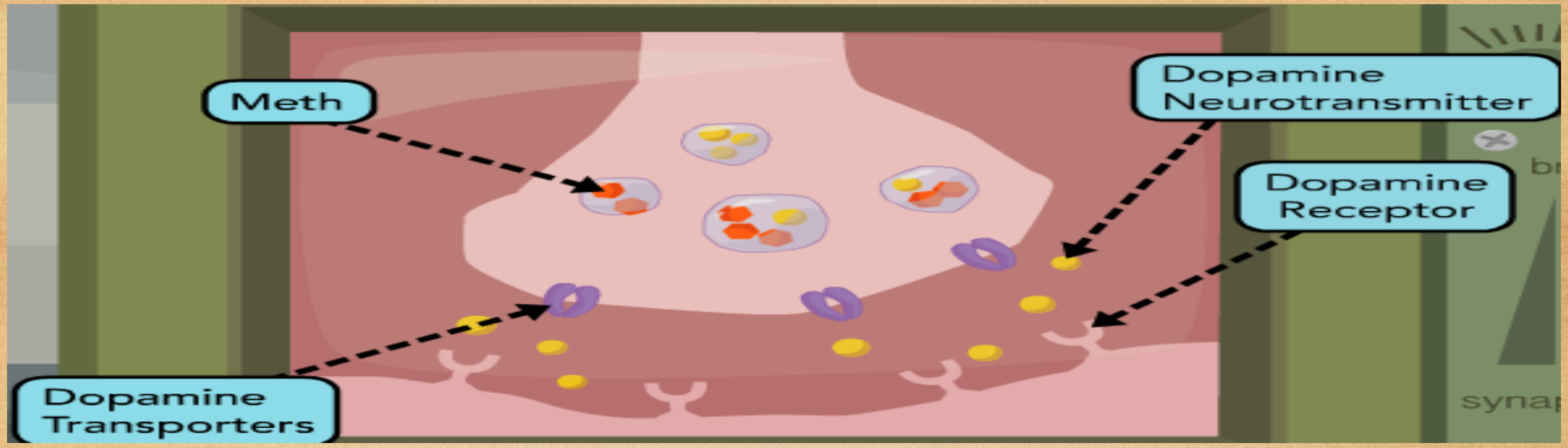
1


Meth
Dopamine Neurotransmitter
Dopamine Receptor
Dopamine Transporters

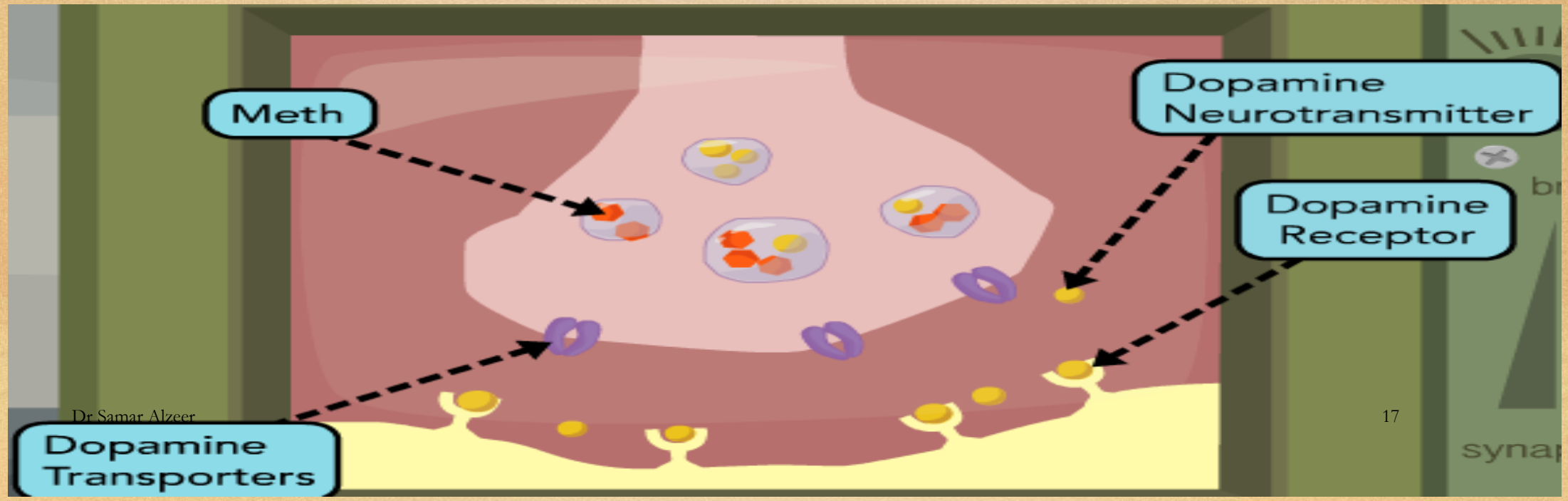
2


Meth
Dopamine Neurotransmitter
Dopamine Receptor
Dopamine Transporters

3


Meth
Dopamine Neurotransmitter
Dopamine Receptor
Dopamine Transporters

4


Meth
Dopamine Neurotransmitter
Dopamine Receptor
Dopamine Transporters

## Absorption

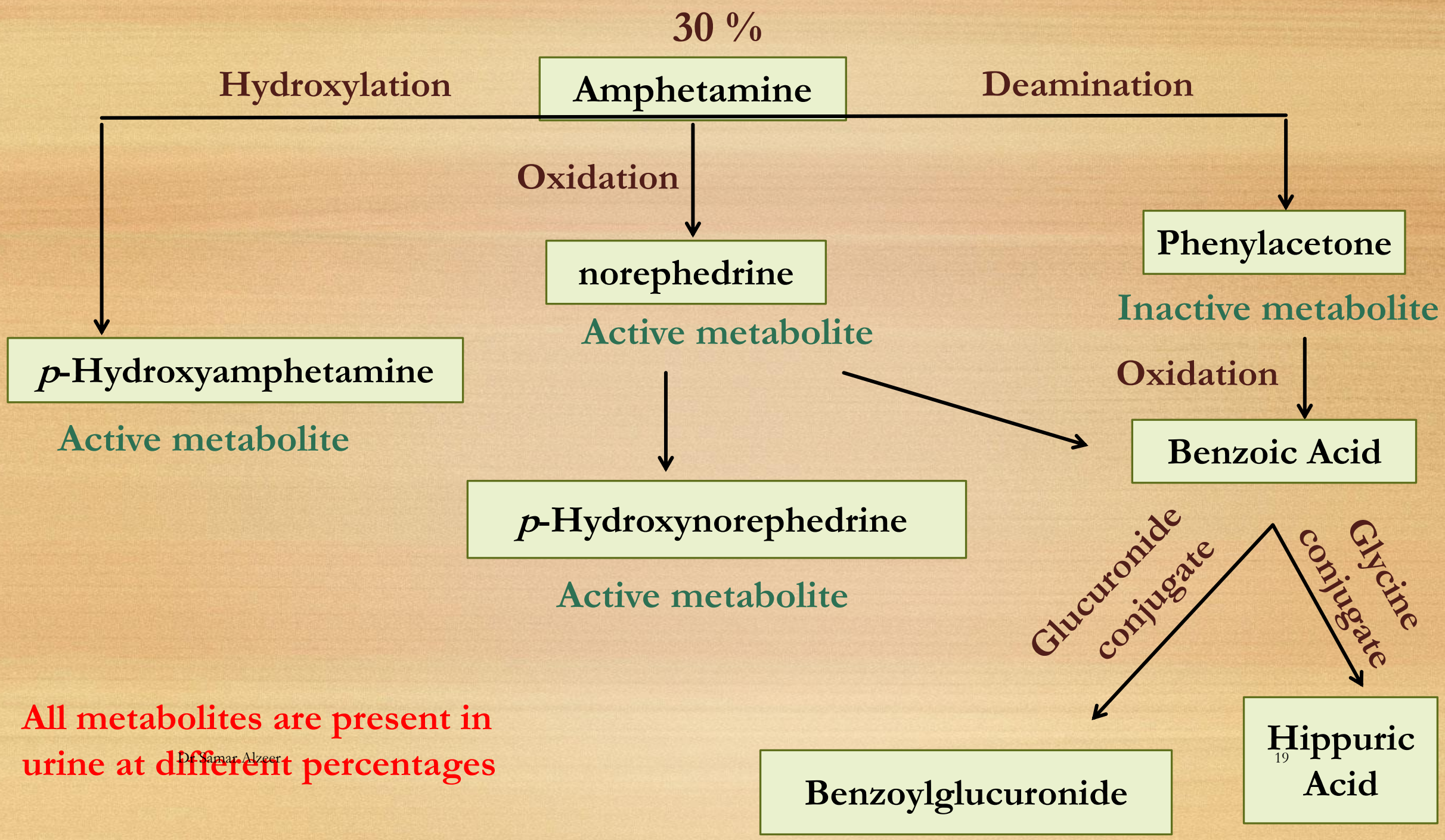
- Onset in 30-60 min
- Reach highest concentration in 2 hours

## Metabolism

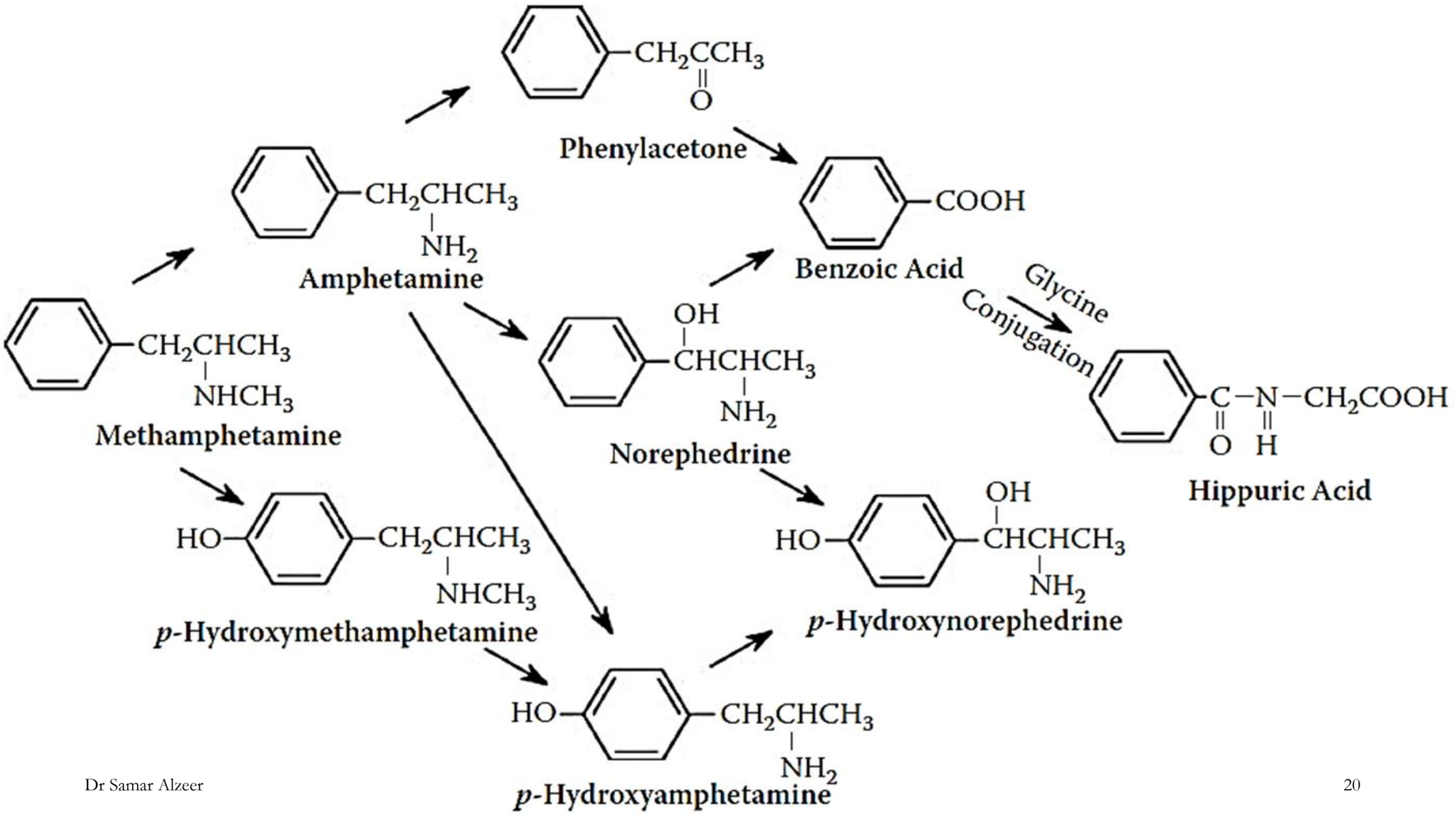
- Oxidation, deamination, hydroxylation

## Elimination

- Eliminated in 3 days
- **Acidic environment:** 74% unchanged drug in urine
- **Basic environment:** 1% unchanged drug in urine
- $T_{1/2}$ is 7-34 hrs . Mean (10-11 hrs)




All metabolites are present in urine at different percentages


Phenylacetone
Amphetamine
Benzoic Acid
Glycine
Conjugation
Methamphetamine
Norephedrine
Hippuric Acid
p-Hydroxymethamphetamine
p-Hydroxynorephedrine
p-Hydroxyamphetamine

Belfast Telegraph

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LATEST: 17:22 Briton stabbed

# Medicine for common cold used to make killer drug crystal meth

Share 10 Tweet 0 ShareThis 355

By Tom Brady
Tuesday, 18 September 2012

Pharmacists in the Republic of Ireland have been put on a nationwide alert to report large sales of over-the-counter medicines, which can be used to manufacture a killer drug.

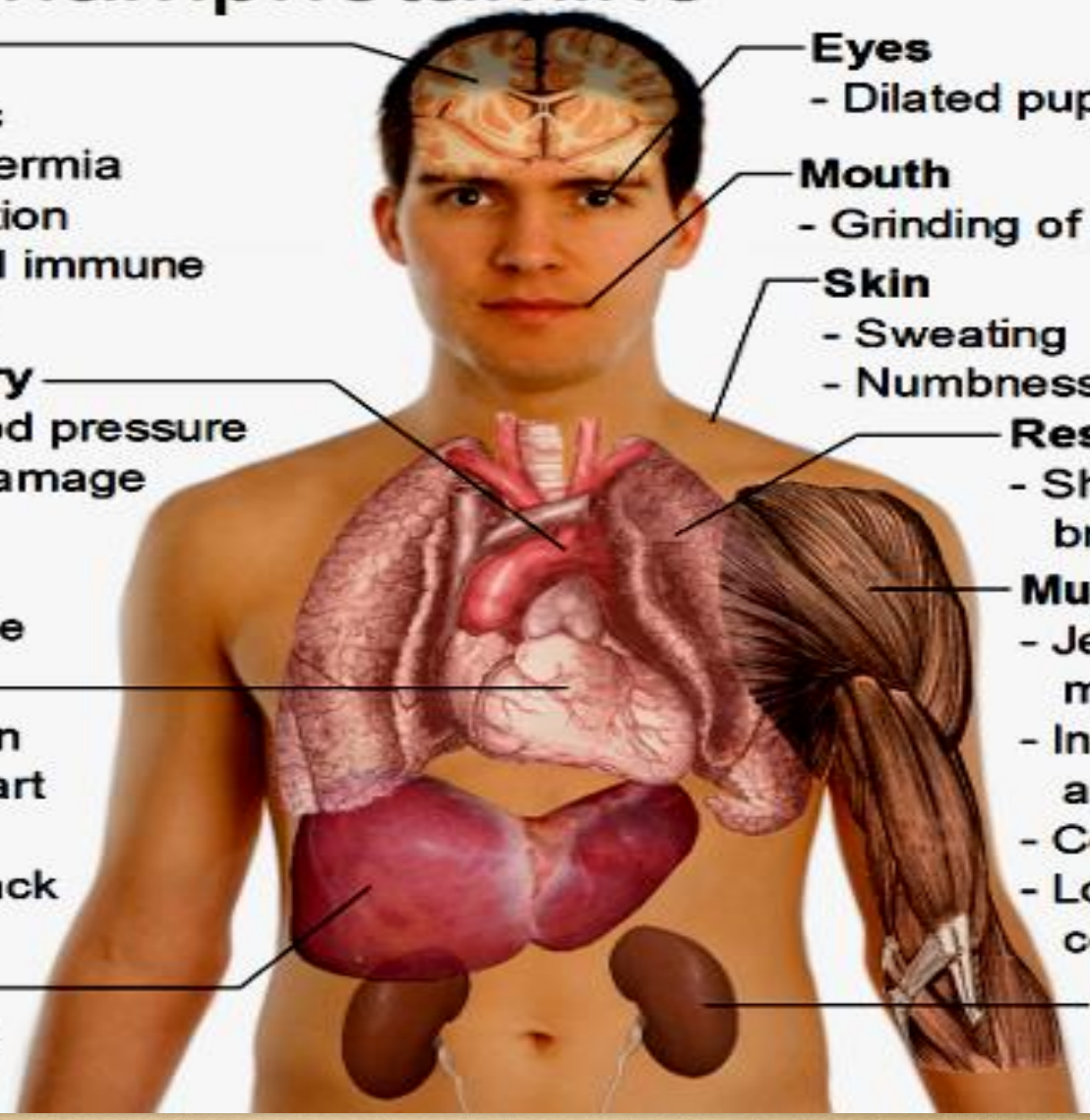
Ads by Google

Analytical Instruments
GC, HPLC, LCMS, Microplate ReadersRefurbished Laboratory Instruments

# Methamphetamine

- It is produced illegally from Pseudoephedrine , ephedrine , or phenylacetone
- P2P method uses phenyl-2-propanone with methylamine
- Illegal drug may have impurities
- Way of use : smoking, i.v. injection , nasal inhalation , tablet
- Methamphetamine is found as :
  - **Free base**: colourless volatile liquid insoluble in water
  - **HCl salt** : white powder soluble in water
  - **Pure crystals** : Crystal Meth

# Adverse (negative) effects of Methamphetamine



**Psychological**
- Insomnia
- Aggressive behavior
- Paranoia
- Incessant conversations
- Decreased appetite
- Increased alertness
- Irritability
- Slurred speech
- Dizziness
- Confusion
- Hallucinations
- Obsessive behaviors
- Depression
- Panic attacks

**Systemic**
- Hyperthermia
- Malnutrition
- Impaired immune system

**Circulatory**
- High blood pressure
- Vessel damage in brain
- Clotting and stroke

**Heart**
- Chest pain
- Rapid heart rate
- Heart attack

**Liver**
- Damage

**Eyes**
- Dilated pupils

**Mouth**
- Grinding of teeth

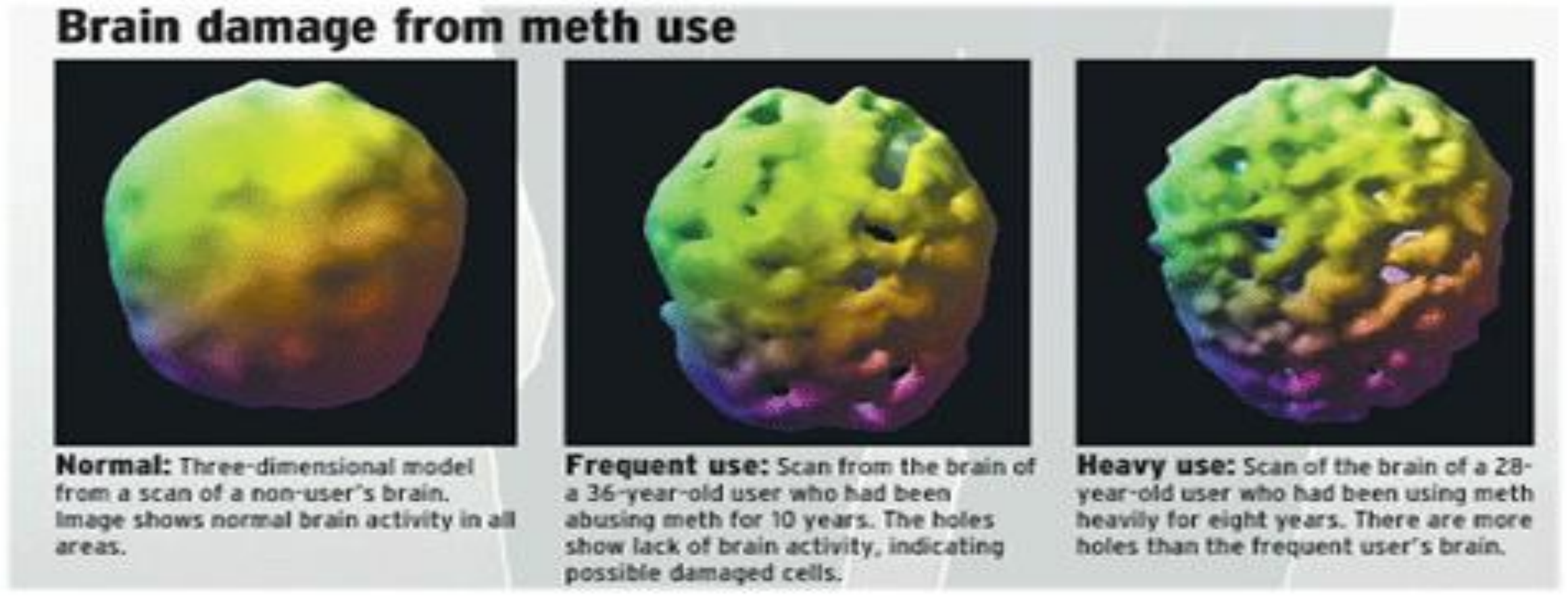
**Skin**
- Sweating
- Numbness

**Respiratory**
- Shortness of breath

**Muscular**
- Jerky movements
- Increased activity
- Convulsions
- Loss of coordination

**Kidneys**
- Damage

# Methamphetamine chronic use




**Limbic system**: emotion, reward

**Hippocampus** : memory


- Dry skin, severe itch
- Severe shrinking of blood vessels
- Acne
- Formication because of hallucination

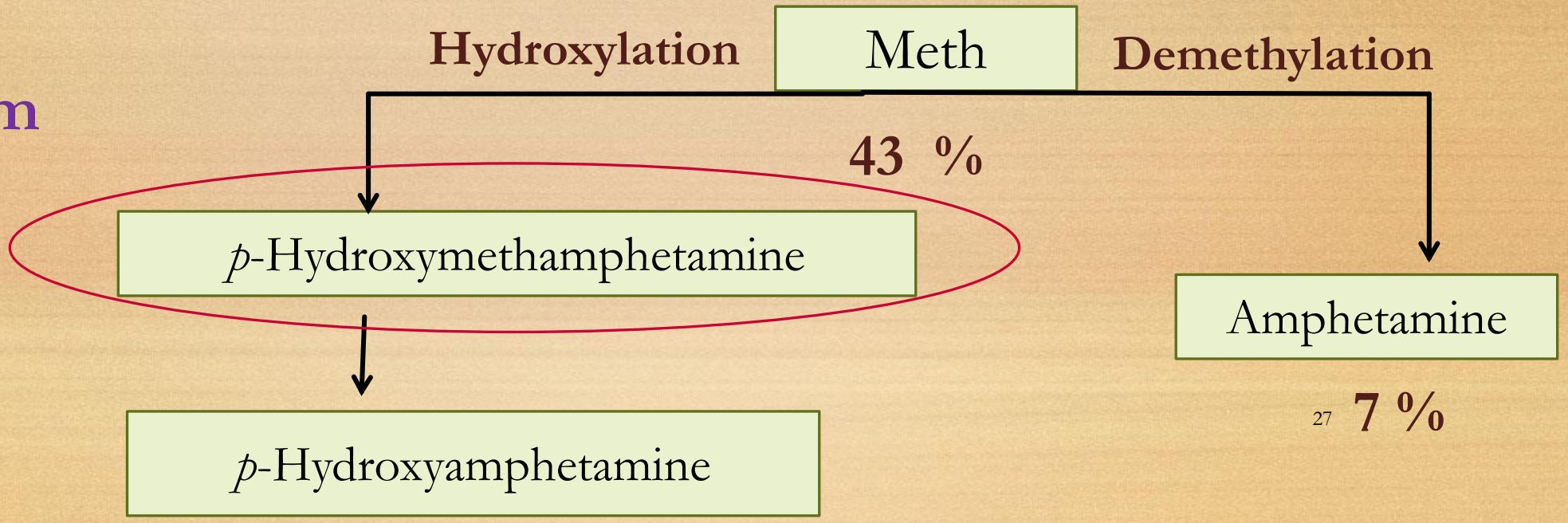
# Meth Mouth

- Dry mouth (xerostomia)
- Bad breath, cavities, and red, swollen gums.
- Severe grinding while using meth.
- Decay of teeth
- Meth causes the vessels that supply blood to oral tissues to shrink
- Meth cause grinding of teeth
- Presence of other chemical substances of acidic nature during meth production

# Methamphetamine

| Absorption | Elimination |
|---|---|
| Immediate action after i.v. injection | **Acidic environment:** 76% unchanged drug in urine |
| 3-5 minutes after smoking | **Basic environment:** 1% unchanged drug in urine |
| 30 minutes after oral use | $T_{1/2}$ : 10-11 hours |

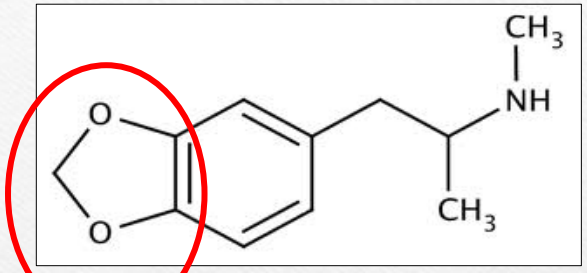
## Metabolism



# 3,4 methylenedioxy methamphetamine (MDMA)

## Hallucinogen: because of methylenedioxy

### Effect on serotonin

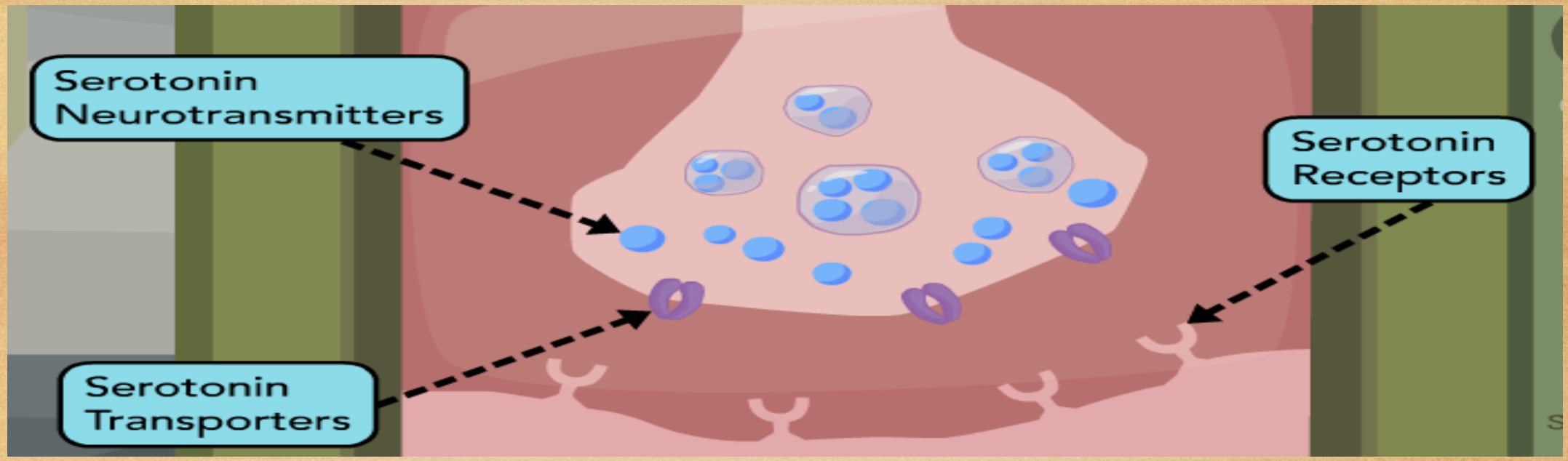



Ecstasy is a modification of meth.

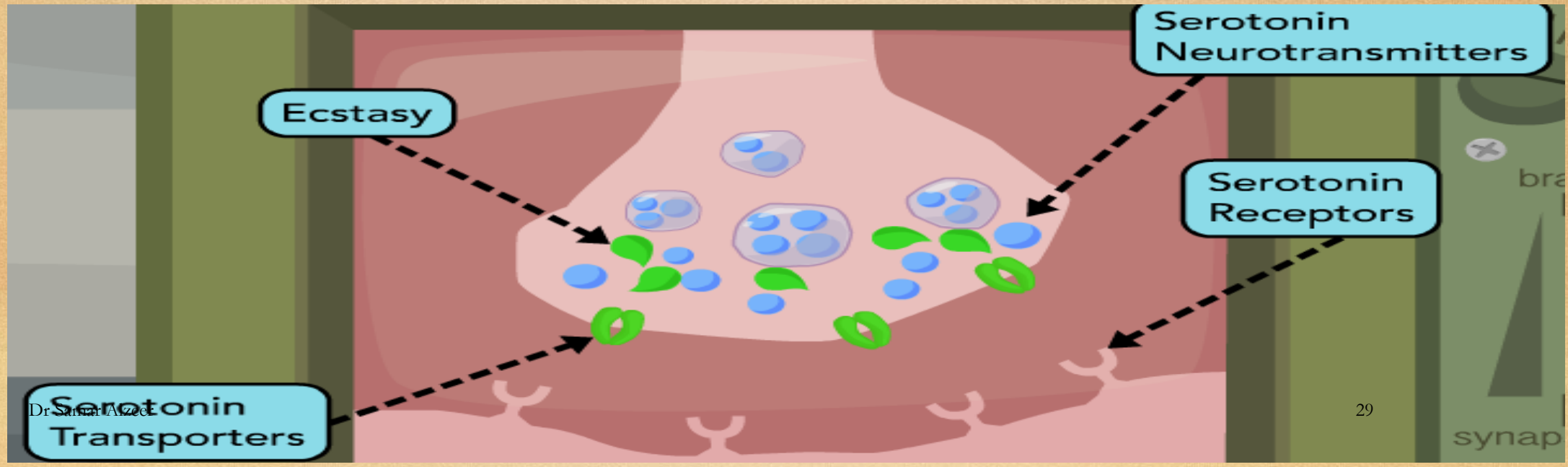

Oral use.
Cannot be smoked

Increase sensation
Talkative
Reduce pain feeling
Increase physical energy

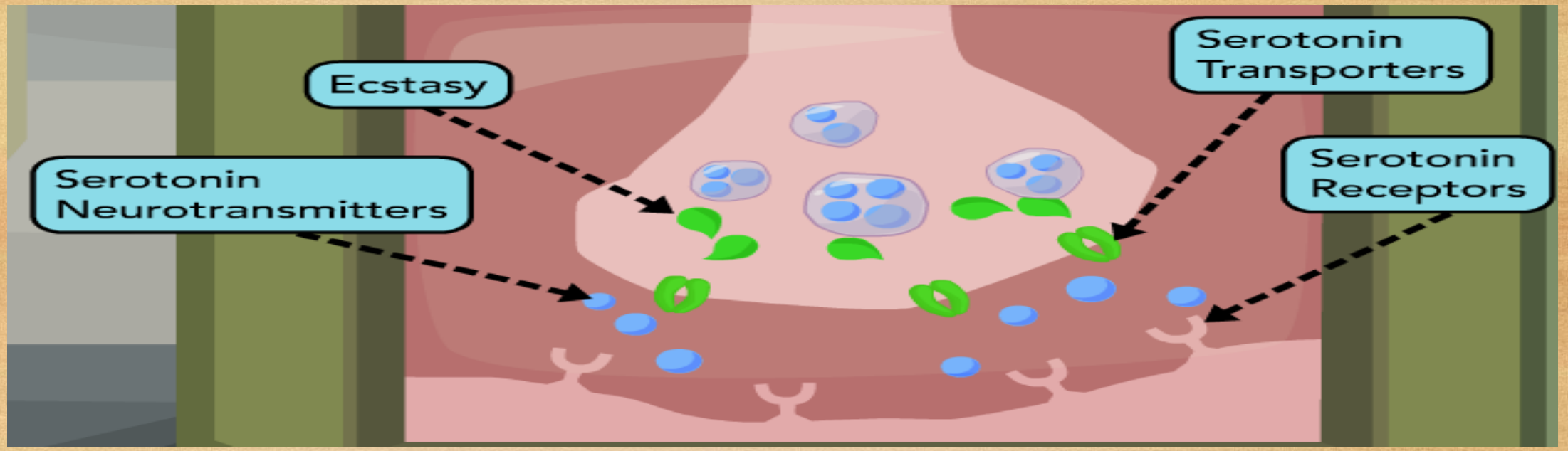
1


Serotonin
Neurotransmitters
Serotonin
Receptors
Serotonin
Transporters

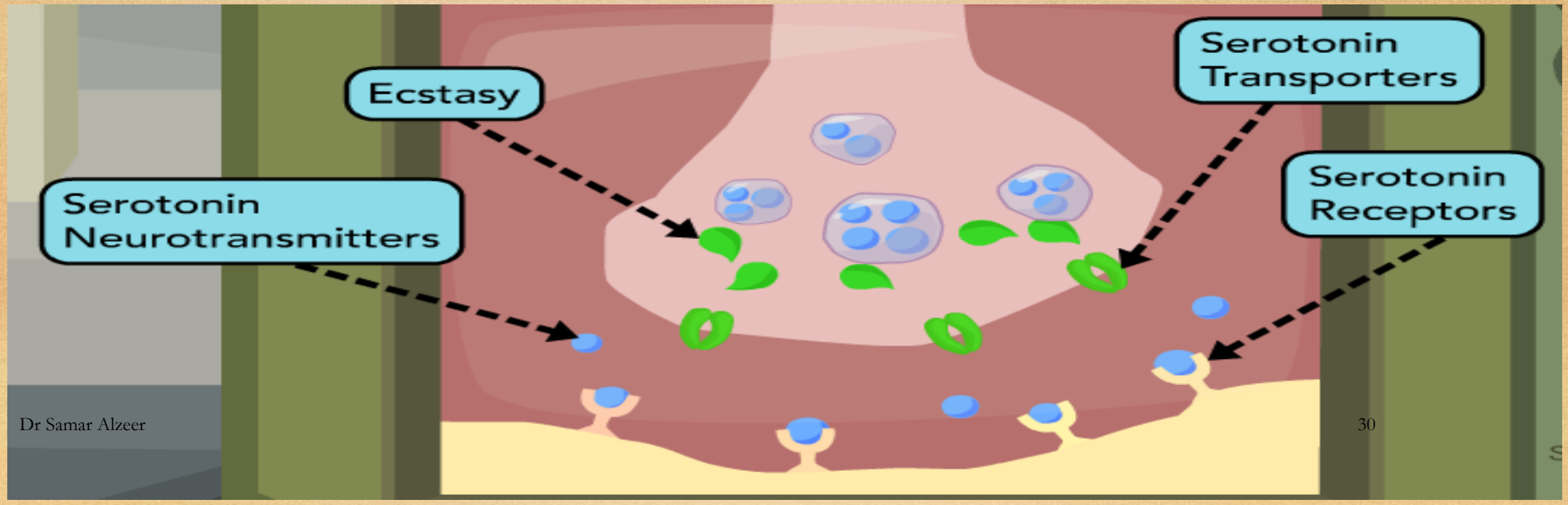
2


Serotonin
Neurotransmitters
Ecstasy
Serotonin
Receptors
Serotonin
Transporters

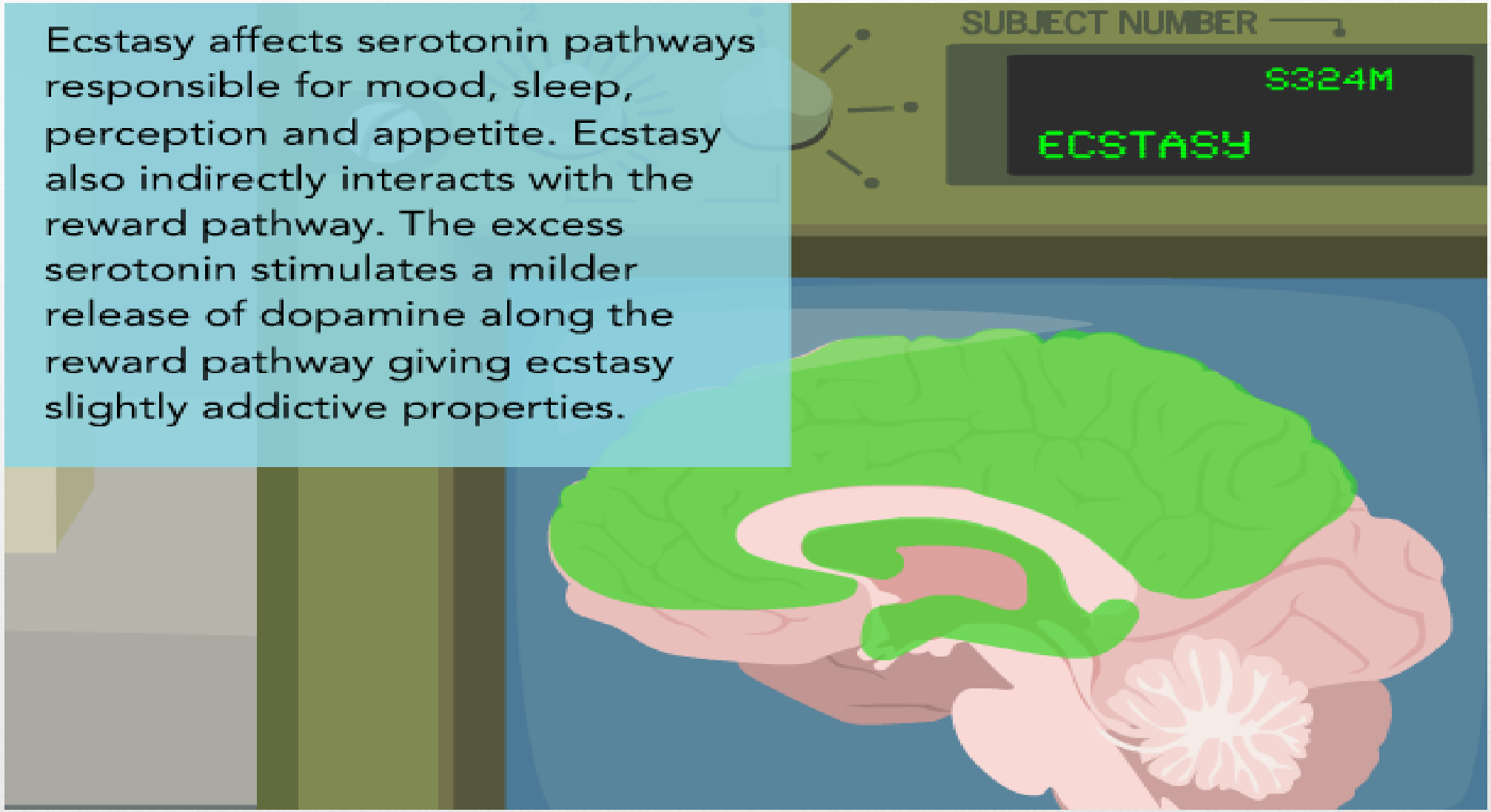
3


Ecstasy
Serotonin Transporters
Serotonin Neurotransmitters
Serotonin Receptors

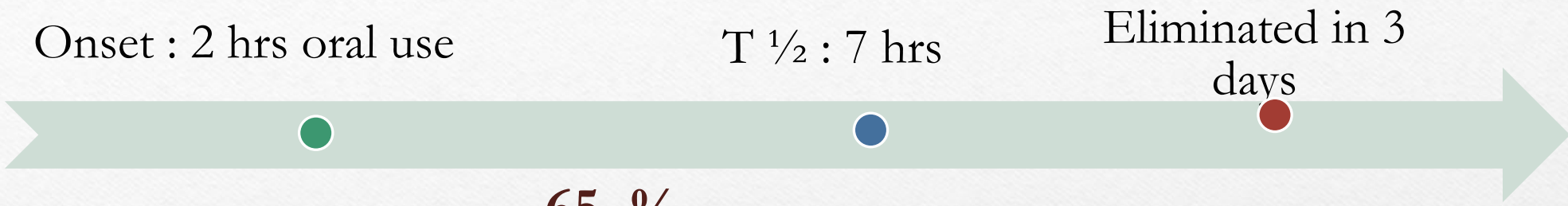
4


Ecstasy
Serotonin Transporters
Serotonin Neurotransmitters
Serotonin Receptors

Ecstasy affects serotonin pathways responsible for mood, sleep, perception and appetite. Ecstasy also indirectly interacts with the reward pathway. The excess serotonin stimulates a milder release of dopamine along the reward pathway giving ecstasy slightly addictive properties.



# 3,4 methylenedioxy methamphetamine (MDMA)




## Metabolism

65 %

MDMA —Demethylation→ MDA

MDA: Active metabolite

MDMA —Hydroxylation→ Hydroxy derivatives

MDA —Hydroxylation→ Hydroxy derivatives

Hydroxy derivatives → Conjugated derivatives (glucuronide & sulfate)

Dr Samar Alzeer

# Detection of amphetamine & derivatives

| Drug | Dose | Window Blood | Window urine |
|---|---|---|---|
| Amph | 5-50 mg | 46 hrs | 1-3 days |
| Meth | 5-15 mg | 48 hrs | 3-6 days |
| MDMA | 50-100 mg | 24 hrs | 2 days |

## Colour tests

**Marquis test ($H_2SO_4$ + formaldehyde)**

Orange colour : amphetamine / Meth

Blue black colour : MDMA

Chromatography

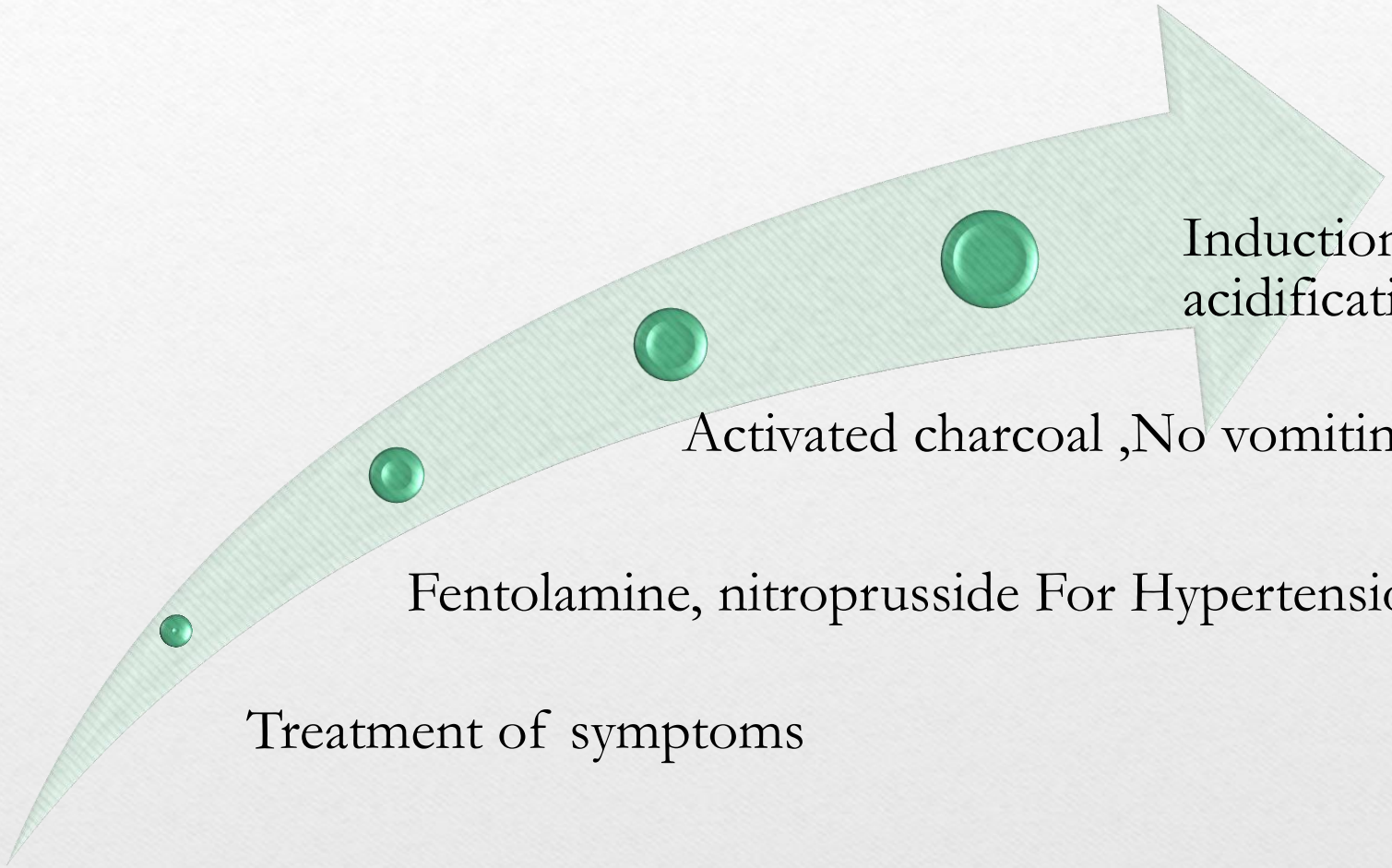
HPLC /

GCMS (derivatisation is required for amphetamine and meth)

# Toxicity & Death from amphetamine & derivatives

- Hypertension & hyperthermia
- Cardiac & hepatic toxicity
- Low therapeutic index. Tolerance can happen after multiple uses
- Meth overdose can lead to blindness because it cuts blood flow to the optic nerve, and makes ulcers in retina. Overdose can cause convulsions, heart attacks , renal failure, brain damage
- Amphetamine & Meth cause addiction
- MDMA doesnot lead to addiction because of hallucinations and adverse effects

# Treatment of Amphetamines toxicity



Induction of elimination by acidification of urine

Activated charcoal ,No vomiting

Fentolamine, nitroprusside For Hypertension , hyperthermia

Treatment of symptoms

# Coroner's Russian roulette alert after student, 18, is killed by ecstasy

- Keen musician Adam Dixon, 18, swallowed the powerful drug with two friends at his halls of residence at Leeds Metropolitan University
- His friends found him 'unresponsive' about four hours after going to bed and paramedics pronounced him dead shortly after
- Teenager's parents warned other youngsters against taking the drug following today's inquest

# British father to face death by firing squad for smuggling crystal meth into Indonesia

By RUTH WHITEHEAD

**PUBLISHED:** 10:14 GMT, 29 September 2012 | **UPDATED:** 15:48 GMT, 29 September 2012

Comments (182) | Share

+1 2 Tweet 13 Like 0

A British father of one has been sentenced to death by firing squad for smuggling drugs into Indonesia, it has emerged.

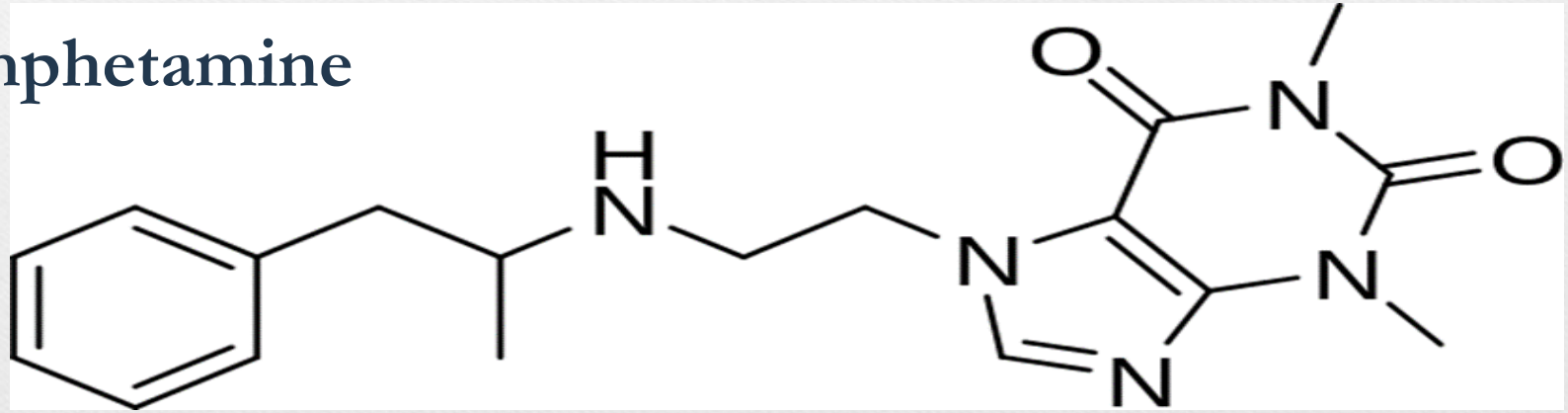
Gareth Cashmore, 33, a roofer from Wakefield, West Yorks, was arreste a year ago after customs officials said they found 6.5kg of methamphetamine – crystal meth – hidden in a compartment in his suitcase

# Fenethylline (Captagon)

- Amphetamine + Theophylline
- Schedule I in USA
- Class C in UK

**Theophylline**

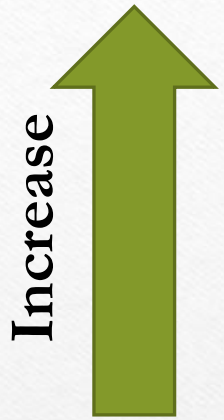
**Amphetamine**



# Fenethylline (Captagon)

- Synthesized in 1961 in Germany
- It was marketed in Europe for 20 years as psychostimulant and analeptic agent under the brand names Captagon, Fitton and Biocapton
- It was used to treat ADHD , narcolepsy , depression

# Fenethylline




Stimulant
alertness
concentration ability
physical performance.


Appetite


Heart rate
Body temperature
Respiration

Blood pressure in small to moderate doses (theophylline is a vasodilator and amphetamine is vasoconstrictor)

# Fenethylline

## Analytical methods & samples

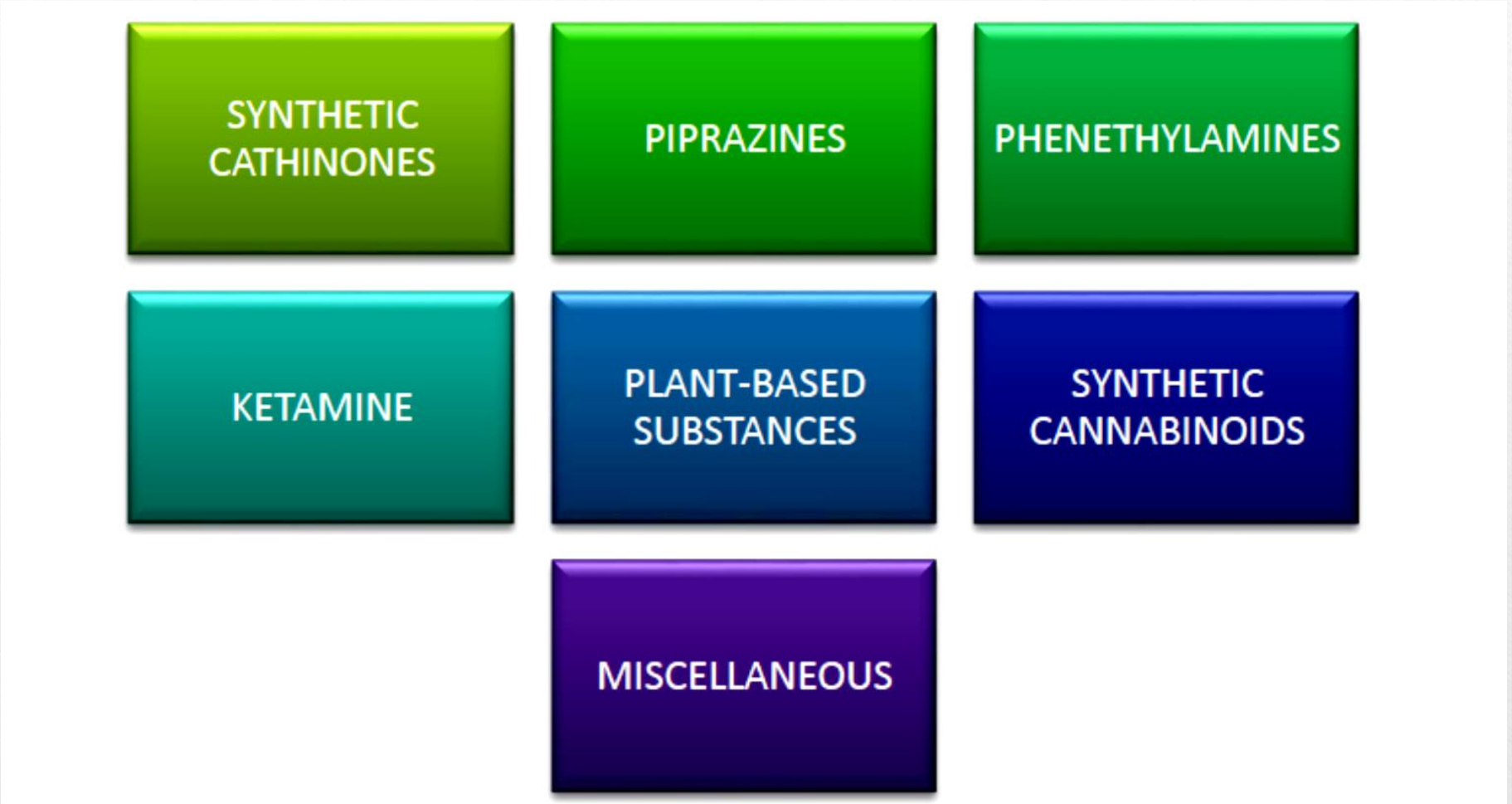
Liquid-liquid extraction then GC/MS.

- Concentrations of fenethylline in hair are more than amphetamine

**Analysis of tablets** by UV, infrared spectroscopy (IR), TLC

**Adulteration of tablets** : Some tablets contain: Amphetamine, caffeine , ephedrine, metronidazole, theophylline, chlorpheniramine, procaine, trimethoprim, chloroquine ,quinine, paracetamol and allopurinol. Zinc , nickel

# NPS classification by the UN

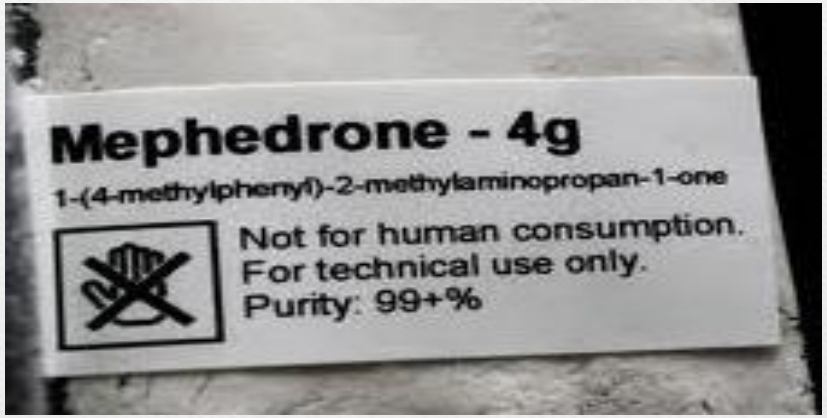


# Mephedrone (4-methylmethcathinone)

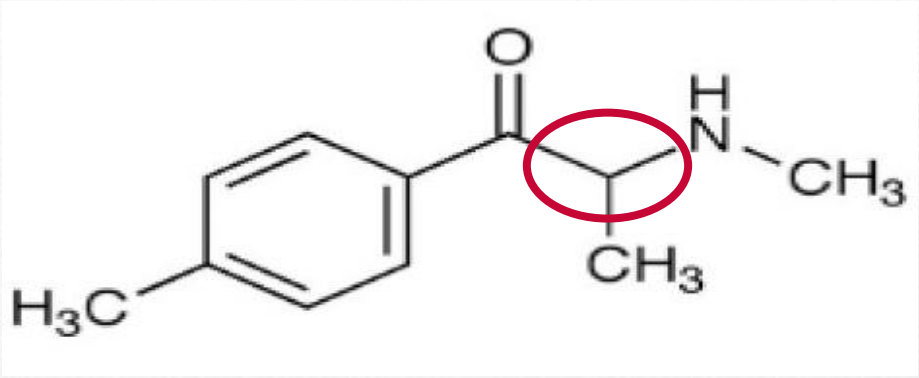
**Bath salts**


**Plant food**

**meow meow.**




**Methedrone** (4-methoxymethcathinone),
**Methylone** (3,4-methylenedioxy-*N*methylcathinone)
**Flephedrone** (4-fluoromethcathinone)




# Mephedrone

| | USA | UK |
|---|---|---|
| **Mephedrone** | Schedule I | Class B |

# Mephedrone

## First reported case of death

18 years old female in Sweden in 2009 .
First diagnosis : Low sodium , metabolic acidosis .
Death after 36 hours  after arriving to hospital

**Two party-goers die after lethal cocktail of former legal high drug 'bubble' and drink during an 'all nighter' with friends**

- Emma Johnston, 21, and Chris Goodwin, 30, died after night out together
- They had taken former legal high mephedrone - otherwise known as bubble
- Pair collapse at separate addresses yesterday after returning from night out
- Three other friends treated for taking a combination of drink and drugs

# Mephedrone

## Synthesis

Starting from
4-methylpropiophenone
or
4-methylephedrine

## Methods of use

- Oral use: Powder form
- Nasal insufflation
- IM / IV Injection
- Rectal use

- Oral dose : 15 and 250 mg
- Nasal insufflation :5 and 125 mg

## Desirable effects

- Euphoria,
- General stimulation
- Enhanced appreciation of music,
- Elevation of mood
- Reduced hostility
- Improved mental function

Similar to cocaine

## Adverse effects

Head rushes, memory problems, altered conscious level ,nasal irritation and bleeds, increased body temperature (often referred to as ‘mephedrone sweat’), chest pain, nausea and vomiting, elevated heart rate, tremors and convulsions, headaches, anxiety, agitation, insomnia and/or nightmares, hallucinations ,delusions

| Absorption | Metabolism | Elimination |
| --- | --- | --- |
| Effect starts minutes after i.v. injection or nasal insufflation | **Demethylation** | No enough information |
| 15-45 minutes after oral absorption / Food affects absorption | **Reduction of keto group** | |
| Effect lasts for<br>2-3 hours /oral<br>30 minutes/ injection | **Tolyl oxidation**<br>$C_6H_5CH_3$ | |

# Mephedrone

**Tolyl oxidation**

hydroxytolyl mephedrone
nor-hydroxytolyl mephedrone

**Reduction of keto group**

nor-dihydro mephedrone
4-carboxy-dihydro mephedrone

**Demethylation**

Normephedrone

nor-dihydro mephedrone

norhydroxytolyl mephedrone

# Mephedrone

## Analytical methods

- Does not give any colour with Marquis test
- Chromatographic techniques : GC/MS , LC/MS/MS
- Nuclear magnetic resonance spectroscopy (NMR) to distinguish the different methyl-methcathinone regioisomers

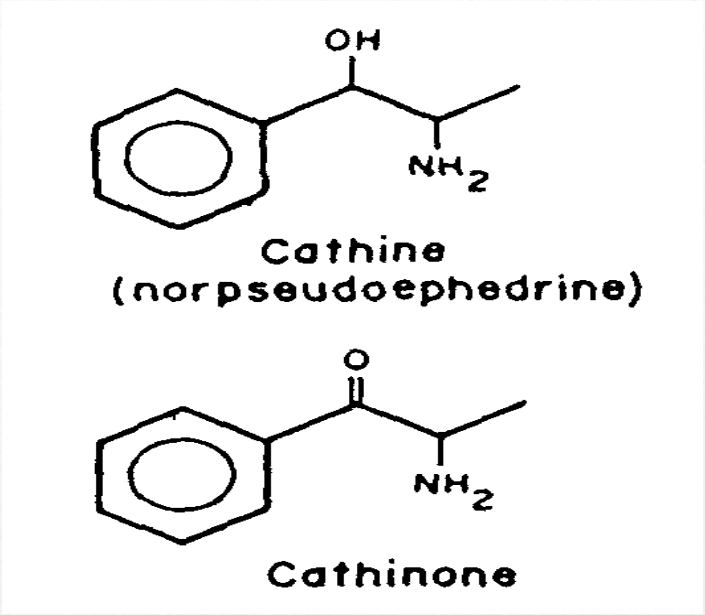
## Toxicity

- Hyperthermia
- Heart palpitation
- Delusions
- Seizures

# Khat

- *Catha edulis*
- Used by chewing

# Khat




norpseudoephedrine

Stronger

Quickly deactivated in the presence of O2

- Cathinone is present at a high concentration in the young leaves, while being converted rapidly in the adult leaves into cathine

- Maximal plasma concentrations of cathinone, after a single oral dose of khat, are attained in about 2 hours; the terminal elimination half-life is about 4 hours
- less than 7% of the ingested cathinone appears in unchanged form in the urine

# Khat

Ecstasy , stimulant , hypertension for 3 hrs

Depression state , anxiety , less concentration

Maybe contaminated by pesticides

Toxicity & Death are rare

**This is khat: The natural high available on British streets...and suspected of funding terrorism**

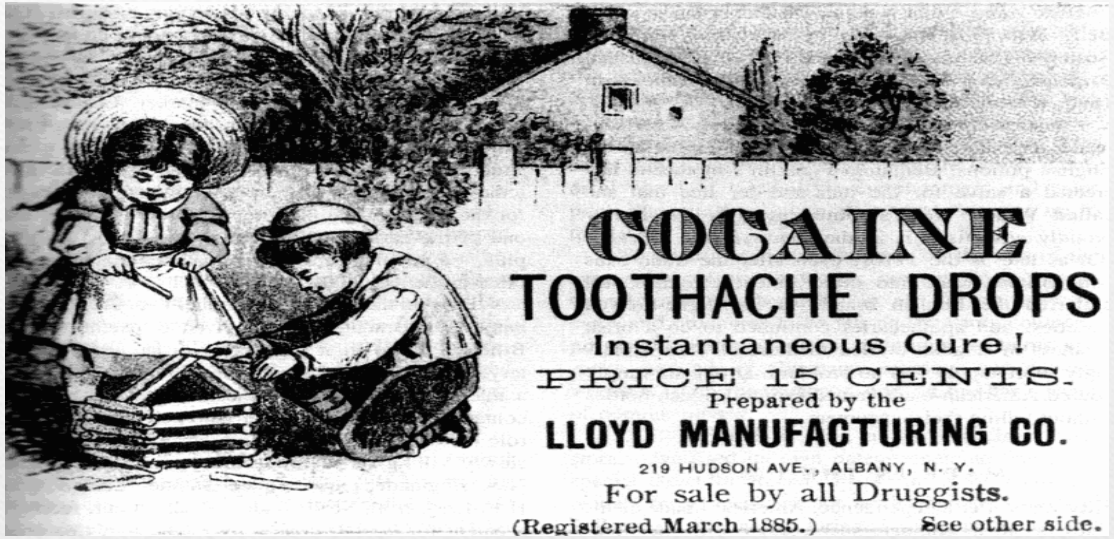
By AIDAN HARTLEY

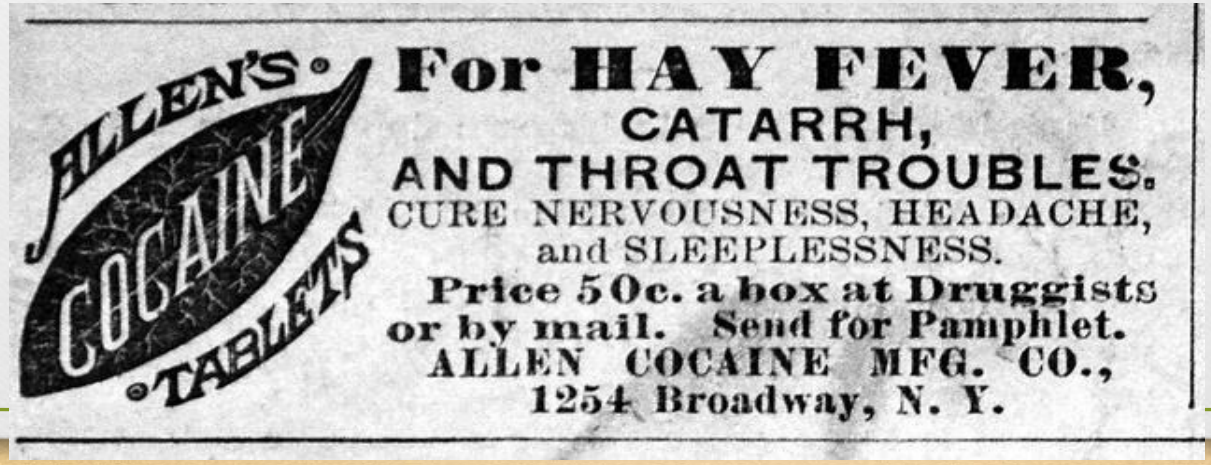
**PUBLISHED:** 21:00 GMT, 16 June 2012 | **UPDATED:** 21:00 GMT, 16 June 2012

Share Tweet +1 Share 1 View comments

**The khat industry in Kenya alone employs 500,000 farmers and dealers – and is worth nearly £80 million a year**

# Cocaine


COCAINE
TOOTHACHE DROPS
Instantaneous Cure!
PRICE 15 CENTS.
Prepared by the
LLOYD MANUFACTURING CO.
219 HUDSON AVE., ALBANY, N. Y.
For sale by all Druggists.
(Registered March 1885.)
See other side.


ALLEN'S
COCAINE
TABLETS
For HAY FEVER,
CATARRH,
AND THROAT TROUBLES.
CURE NERVOUSNESS, HEADACHE,
and SLEEPLESSNESS.
Price 50c. a box at Druggists
or by mail. Send for Pamphlet.
ALLEN COCAINE MFG. CO.,
1254 Broadway, N. Y.

# Cocaine

- **Semi synthetic drug**

| USA | UK |
|---|---|
| Schedule II | Class A |

## History

- **1859** : isolation of cocaine from the coca plant by Albert Niemann
- **1884** : Use of cocaine as local anesthetic in eye surgery by Karl Koller
- **1884** : Book (about Coca) by *Sigmund Freud*
- **1887-1894** : overdoses and death related to cocaine
- Cocaine was used previously in cocacola & is present at low level in coca tea

# Cocaine Extraction

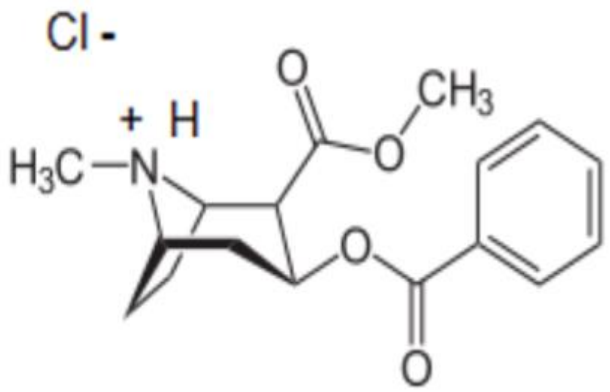
Coca plant
Erythroxylum Coca

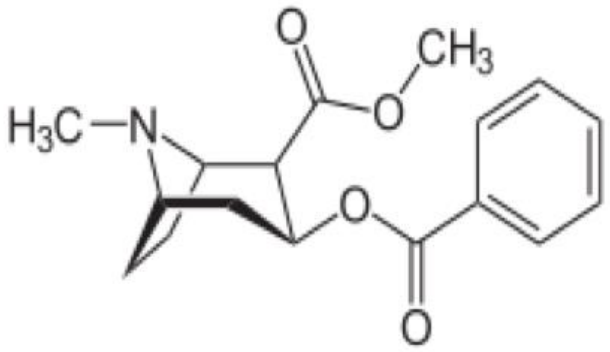
Extraction of crude coca paste from coca plant

Purification of coca paste to cocaine free base

Conversion of free base to cocaine HCL salt

# Cocaine




benzoylmethylecgonine

**Powder Cocaine**

**Crack Cocaine**

**Cocaine salt**

**Cocaine free base**

# Cocaine

## Crack Cocaine

**Smoking**

Crack cocaine = free base cocaine + baking soda+ Water

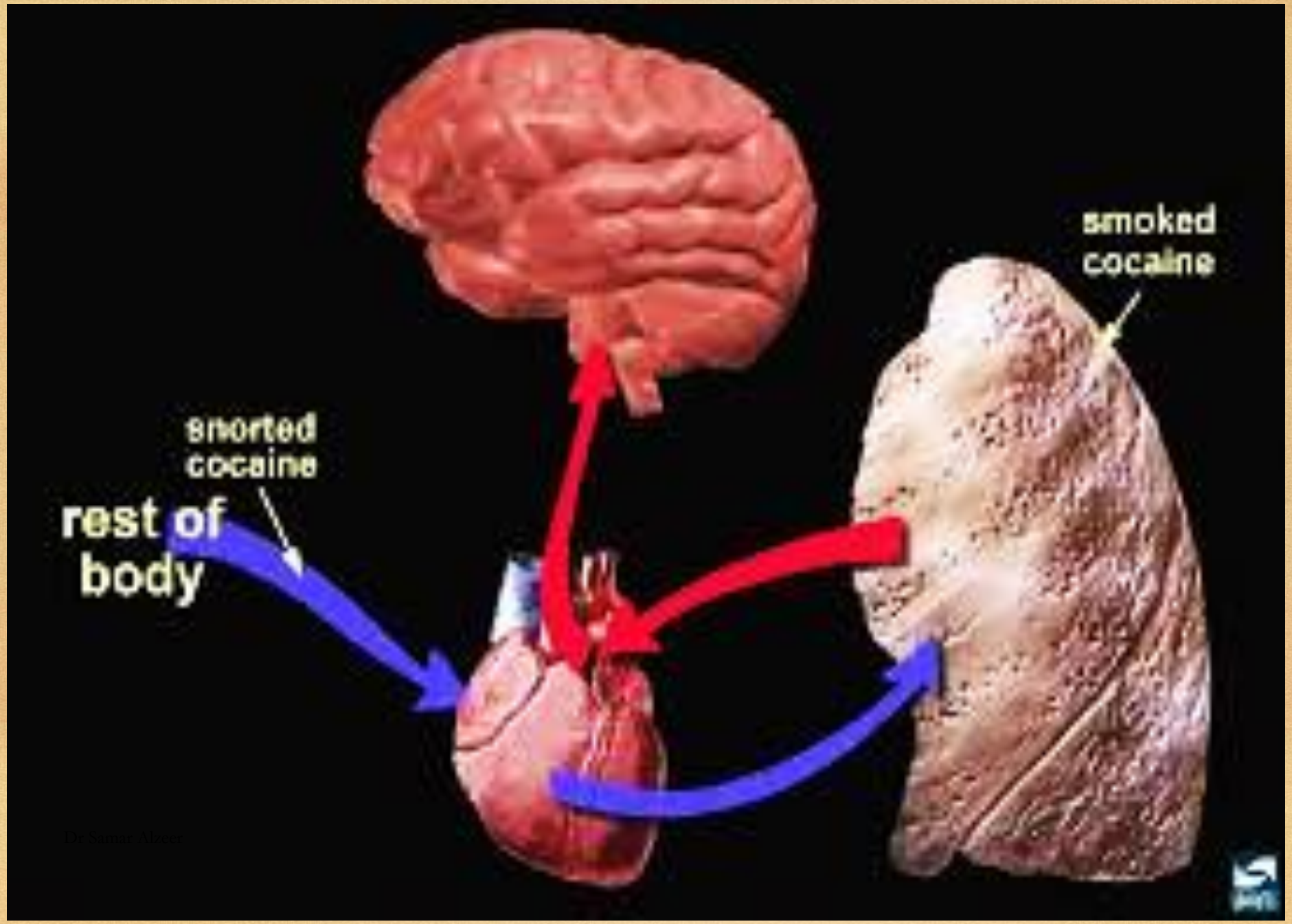
**100–150 mg**

## Cocaine salt

**Snorting**

**i.V injection**

**20–30 mg**


smoked
cocaine
snorted
cocaine
rest of
body

# Cocaine

## Medical uses

local anesthetic in eye, ear, nose & throat surgeries

Treatment of tonsillitis , dental pain, burns, hay fever , hemorrhoids

## Desirable Uses

Increase concentration, energy. Reduce appetite

Increase social communication, self-confidence, and mood

## Adverse effects

anxiety, depression, nervousness, tolerance & addiction

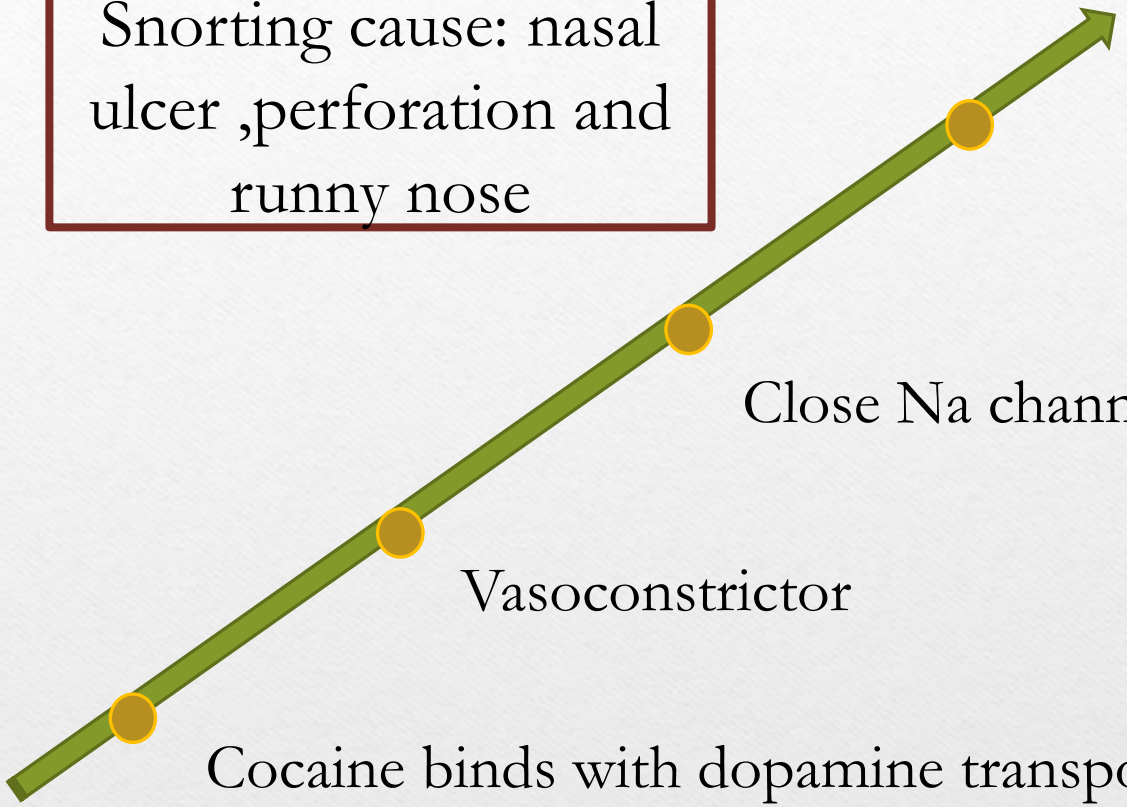
# Ophthalmic Anaesthesia

## Local anaesthetic agents and adjuvants

- **Epinephrine**: when added to cocaine, was found to extend useful anaesthesia time with cocaine, decrease vitreous pressure, decrease bleeding, and decrease the dose needed. Because cocaine worked even better when epinephrine was added, the search for an 'ideal' ophthalmic LA gained little momentum.
- **Procaine** (originally named novocaine): cocaine was replaced by procaine after 1905 in general surgery because it was safer. Procaine became more effective when epinephrine was added to obtain

# Mechanism of Toxicity

Snorting cause: nasal ulcer ,perforation and runny nose



Affect brain centre responsible for voluntary movements. **Symptoms**: Continuous movement and inability to stay still

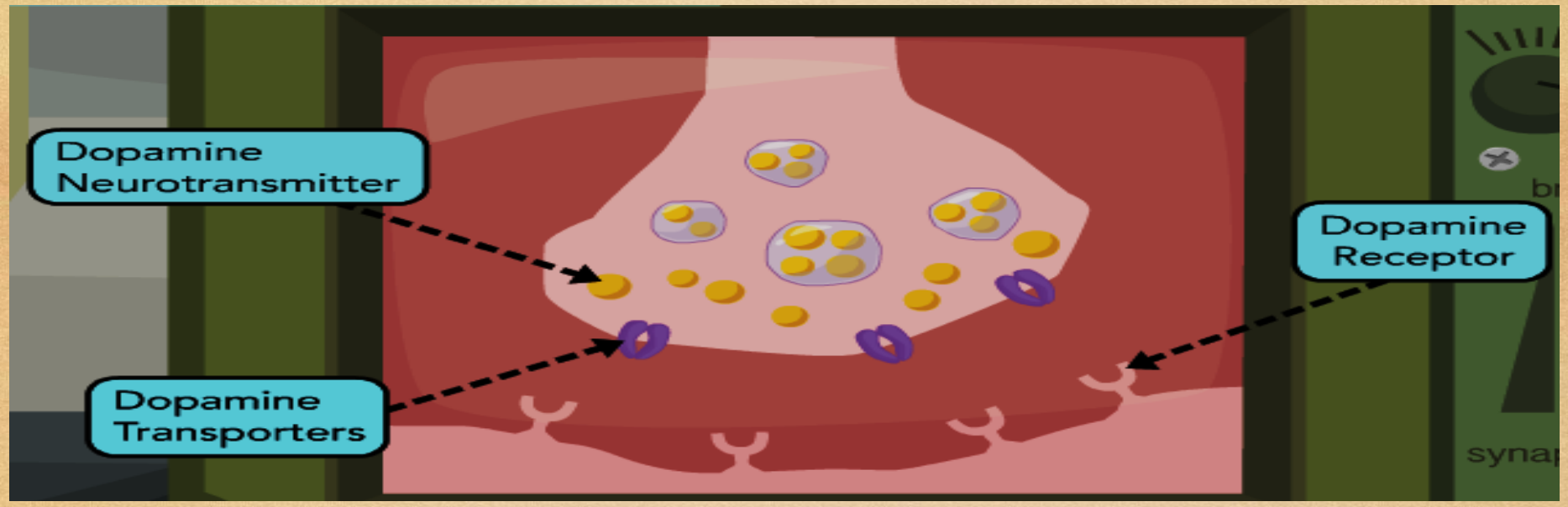
Close Na channels so cause numbness

Vasoconstrictor

Cocaine binds with dopamine transporters so increases dopamine levels. It is CNS stimulant so increase noradrenaline

# Effect on Dopamine

1

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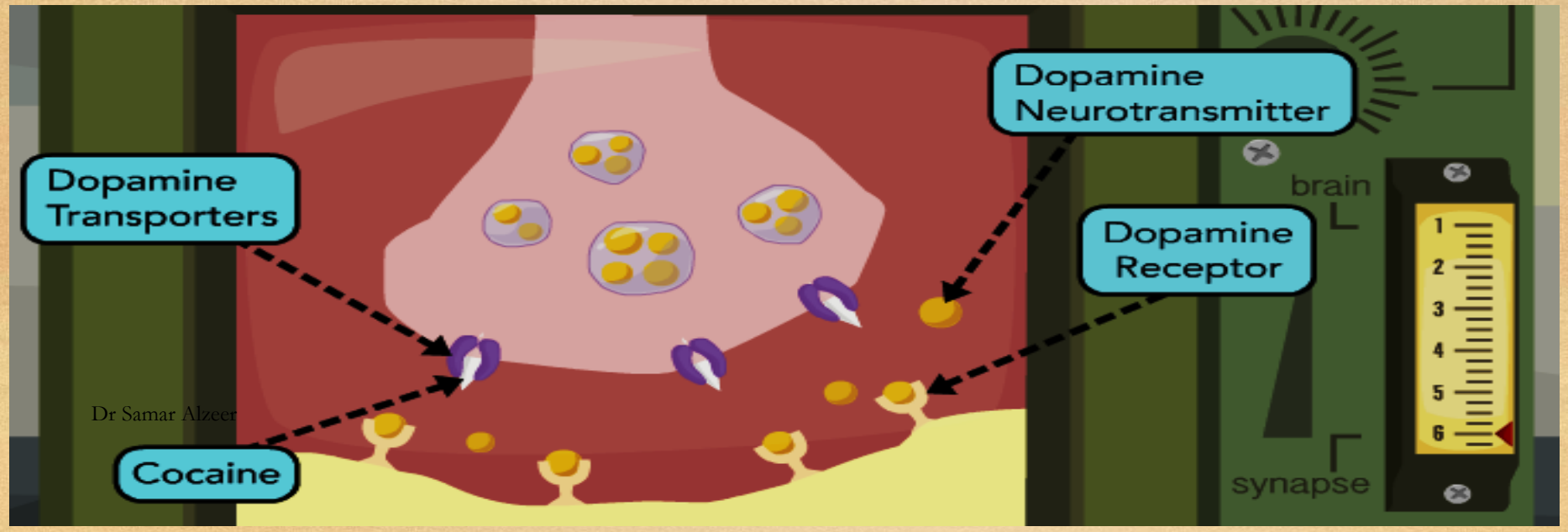



**Bind to dopamine transporters**

# Cocaine

## Absorption

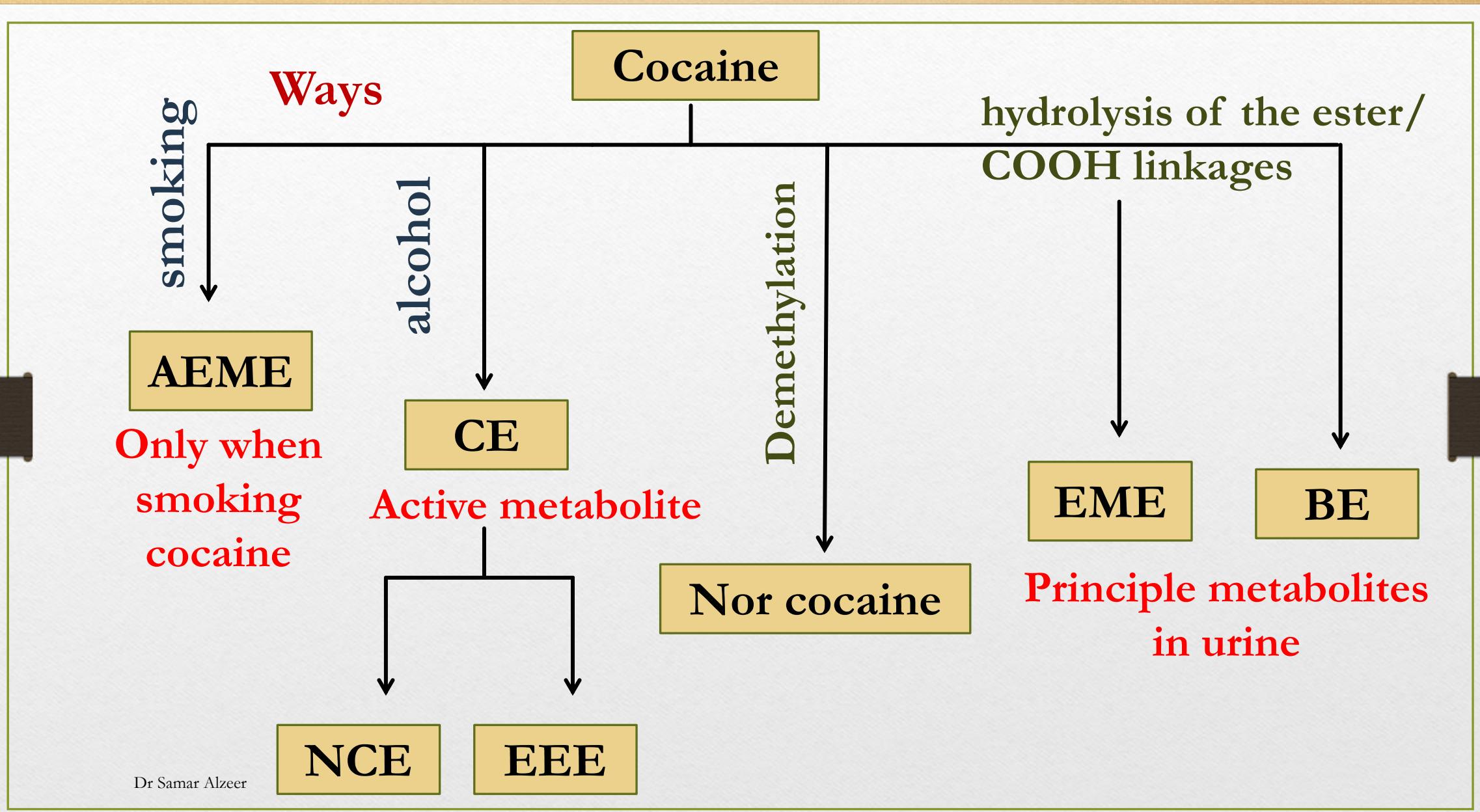
- Bioavailability by nasal route 97 %
- Bioavailability by smoking route 70-80 %
- Onset : 2 min after smoking / i.v injection
- Onset: 20-30 min after oral or nasal consumption because of vasoconstriction

## Distribution & Metabolism

- Protein binding : 90 %
- Metabolized by hydrolysis or demethylation
- Cocaine + alcohol = Cocaethylene which passes BBB

## Elimination

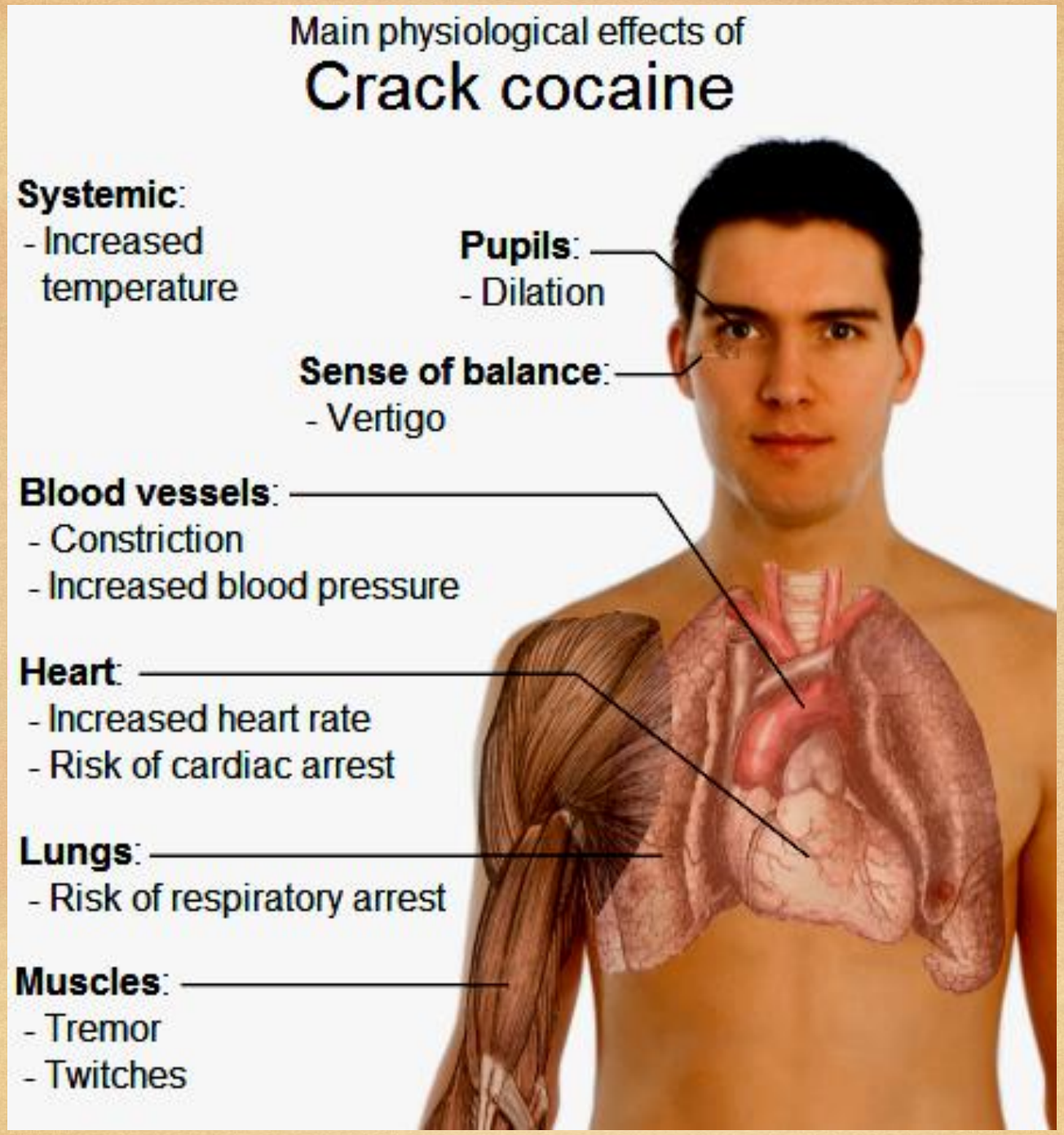
- Half life : 1 hour for parent drug / 4-5 hrs for metabolites
- Elimination : 90% by urine
- 1-10% unchanged in urine according to urine pH

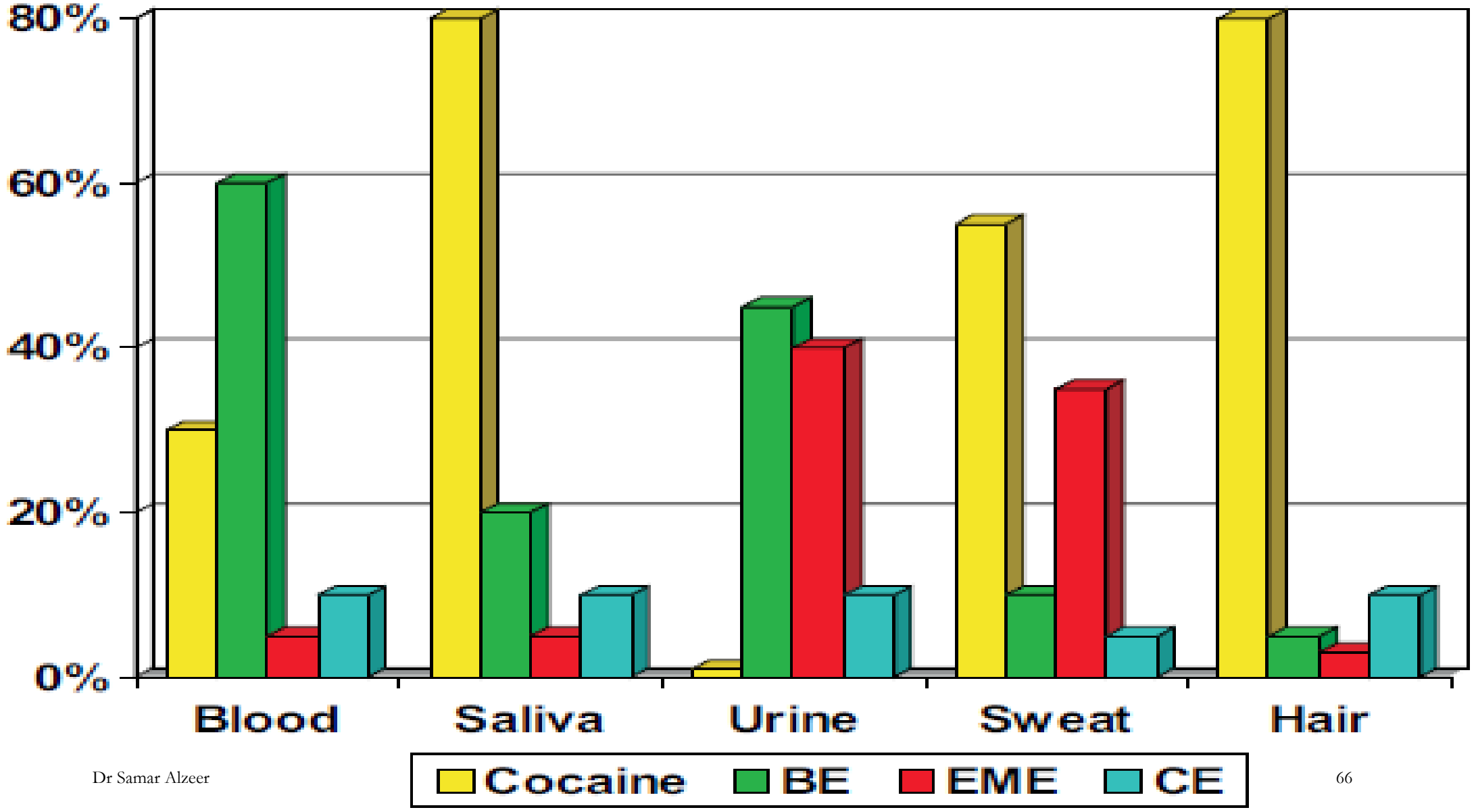

Cocaine
Ways
smoking
alcohol
Demethylation
hydrolysis of the ester/ COOH linkages
AEME
Only when smoking cocaine
CE
Active metabolite
NCE
EEE
Nor cocaine
EME
BE
Principle metabolites in urine
Dr Samar Alzeer

| | |
|---|---|
| **BE** | **Benzoylecgonine** |
| **EME** | **Ecgonine Methyl Ester** |
| **CE** | **Cocaethylene** **Cross BBB** |
| **EEE** | **Ecgonine ethyl Ester** |
| **NCE** | **Nor Cocaethylene** |
| **AEME** | **Anhydroecgonine methyl ester** |

Main physiological effects of

# Crack cocaine




80%
60%
40%
20%
0%
Blood
Saliva
Urine
Sweat
Hair
Cocaine
BE
EME
CE

# Detection of Cocaine

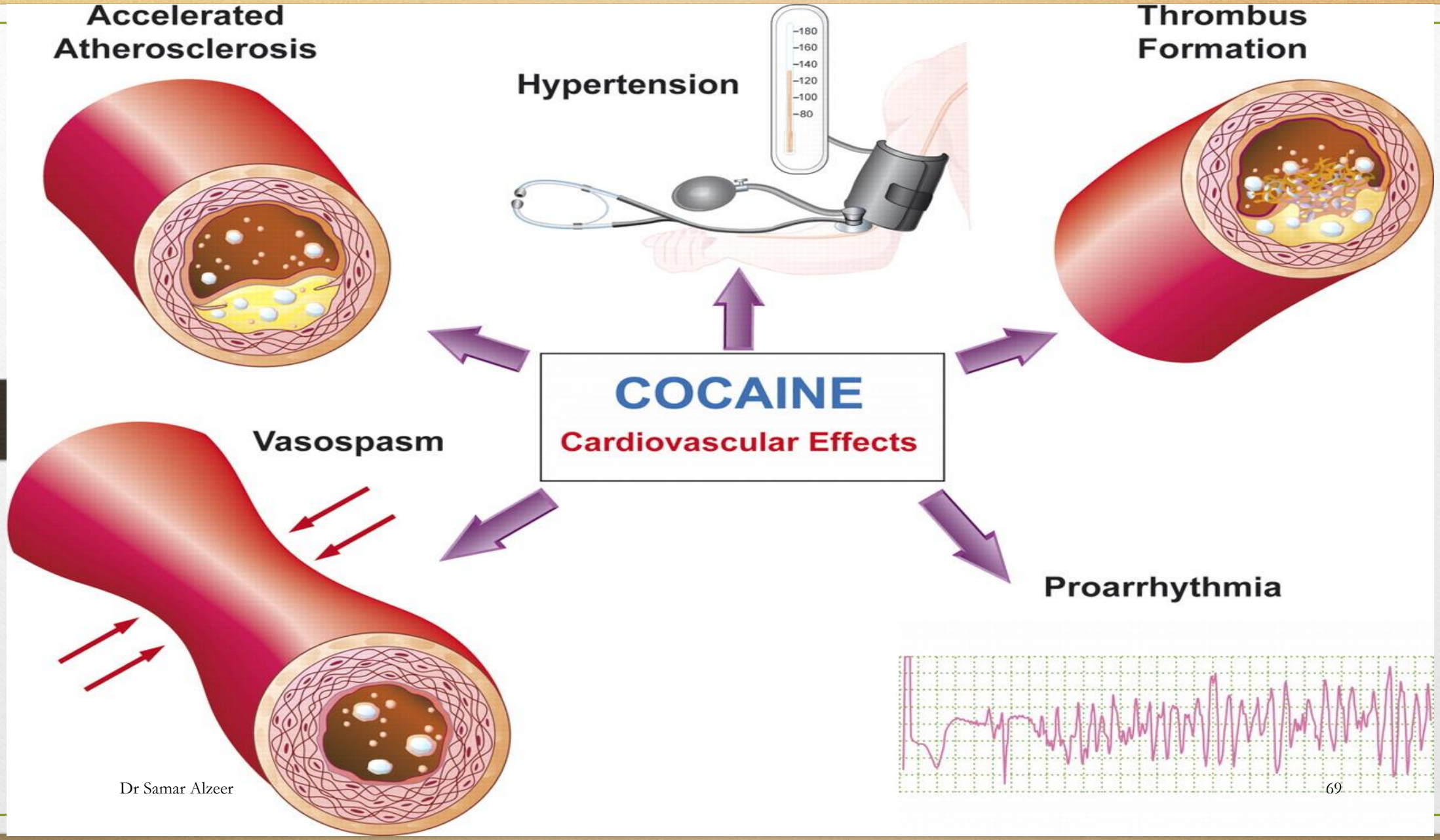
Cocaine dose by nasal route : 20-100 mg

| Compound | Window of detection in blood | Window of detection in urine | Window of detection in saliva |
|---|---|---|---|
| **Cocaine** | 12 hrs | 24 hrs | 5-12 hrs |
| **Benzoylecgonine** | 48 hrs | 48-72 hrs | 12-24 hrs |

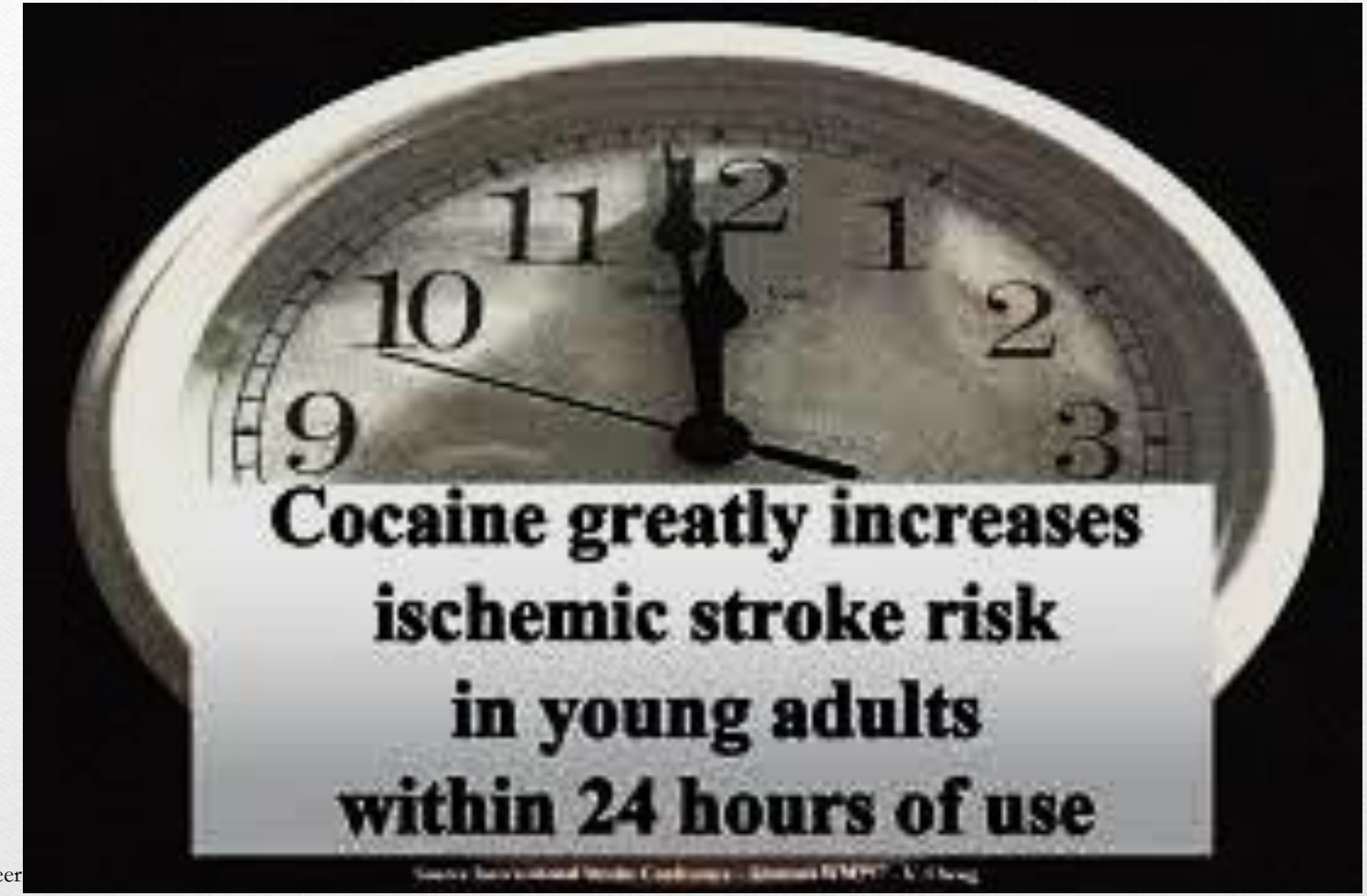
| | |
|---|---|
| **Colour tests** | Scott reaction with cobalt(II)- thiocyanate : blue colour |
| **Chromatography** | HPLC / GC |
| | IR Spectroscopy to distinguish HCL cocaine from free base |
| | Liquid-liquid extraction to distinguish HCL cocaine from free base |

# Overdoses & Death

- Toxicity happens quickly when smoking or injecting cocaine, slowly when taking it orally or by nasal route
- Hypertension & hyperthermia
- Cardiovascular toxicity: arrhythmia , myocardial necrosis
- Cocaine users may have Nasal septal perforation, chest pain , necrotic ulcers
- Treat hypertension with propranolol with phentolamine (vasodilator
- Changing urine pH does not effect cocaine elimination because of quick distribution & metabolism


Accelerated Atherosclerosis
Hypertension
Thrombus Formation
COCAINE
Cardiovascular Effects
Vasospasm
Proarrhythmia

# Overdoses & Death



# Forensic Toxicology

# Drugs of Abuse –2–



Dr Samar Alzeer

# Recreational Drugs

# Hallucinogens

# Hallucinogens or Psychedelic drugs

Hallucinogens are a group of drugs that have the capacity to alter perceptual, cognitive and emotional states. They can alter consciousness in profound and bizarre ways.


# Hallucinogens classification

**Chemical Structure**

**Hallucinogens**

- **Tetrahydrocannabinoids** →
  - Marijuana
  - Hashish
- **Indolealkylamines /Tryptamines** →
  - Methoxydimethyltryptamine
  - Dimethyltryptamine
  - Psilocin
  - Psilocybin
- **Phenylethylamines** →
  - Mescaline
  - MDMA
- **Ergot alkaloids** (Lysergamides) → LSD

# Hallucinogens classification

## Functional

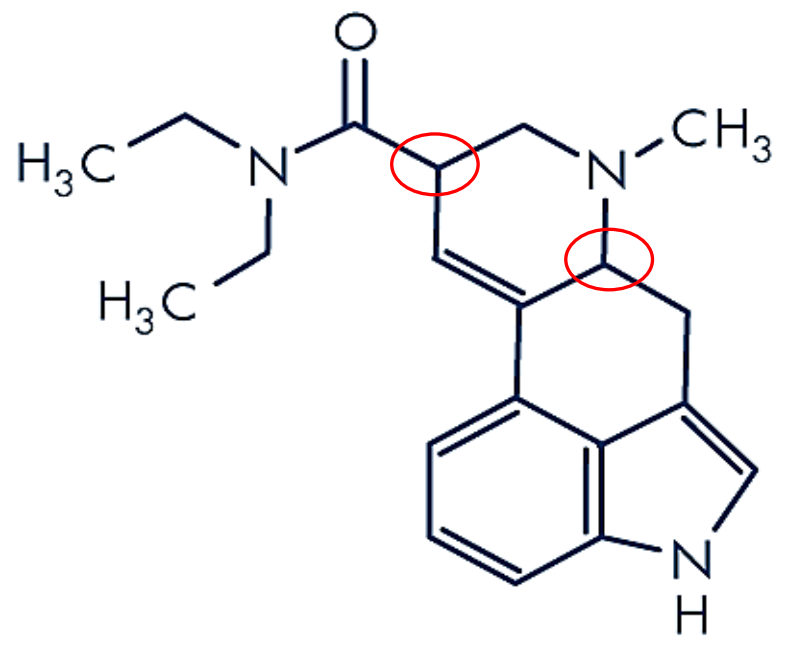
**Hallucinogens**

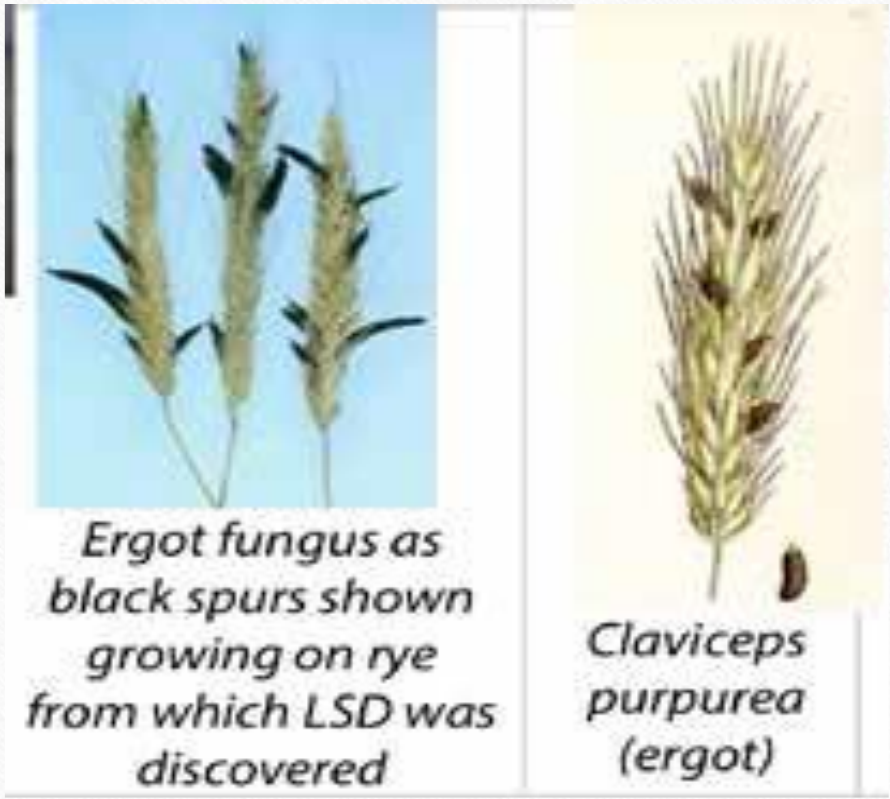
- Serotonergic hallucinogens
  - LSD
  - Mescaline
  - Psilocybin
- Methylated amphetamines
  - MDMA
- Anticholinergic hallucinogens
  - Atropine
  - Scopolamine
- Dissociative anaesthetics
  - Ketamine
  - PCP

# Classification

| Substance | USA | UK |
|---|---|---|
| LSD | Schedule I | Class A |
| Mescaline | Schedule I | Class A |
| Psilocybin | Schedule I | Class A |
| Cannabis | Schedule I (By state) | Class B (allowed medical marijuana) |
| PCP | Schedule II | Class A |
| Ketamine | Schedule III | Class B |
| | | |

# Lysergic acid diethylamide (LSD)



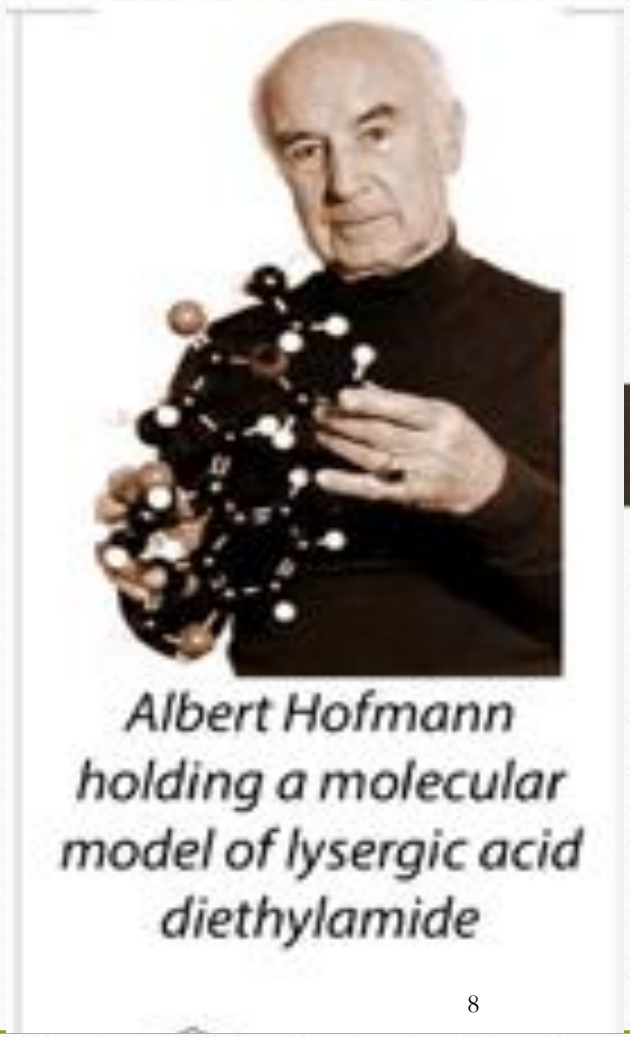



*Ergot fungus as black spurs shown growing on rye from which LSD was discovered*

*Claviceps purpurea (ergot)*

# Lysergic acid diethylamide (LSD)

- It was synthesized by Albert Hofmann in 1938
- Semi-synthetic drug
- Lysergic acid is one of several alkaloids contained in ergot, a parasitic fungus that infects grain, especially rye
- Colourless, odourless and tasteless
- Stronger hallucinogen to date



Albert Hofmann holding a molecular model of lysergic acid diethylamide

# Lysergic acid diethylamide (LSD)

**1938**

Synthesis of LSD

**1943**

Hallucinogenic effects known

**1966**

LSD banned

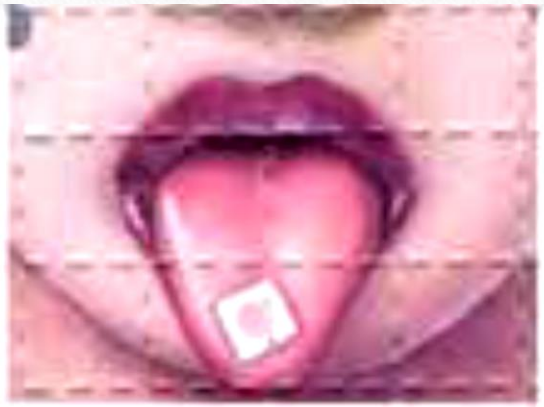
**1990s**

Return of LSD

| UK | USA |
|---|---|
| A | Class I |

# Lysergic acid diethylamide (LSD)

- liquid, powder, and microdot dosage form, liquid-impregnated blotter paper, gelatine squares
- Common name: **acid**
- **Dosage** : 20-80 µg
- Effect lasts for 8-12 hours



*LSD commonly added to blotting paper 20-80 µg is sufficient for first-time users.*

**Sensory effects**: Colours, smells, sights and sounds become more intense and often distorted so that people might hear colours and see sounds

**Hallucinations**: Distortions in shapes and movements and an altered sense of time, a person's perception of reality are distorted leading to a wandering in the mind.

**Physiological effects:**

- Elevated blood pressure
- increased heart rate
- feelings of dizziness
- loss of appetite,
- dry mouth,
- sweating, nausea,
- dilated pupils,
- blurred vision
- tremors

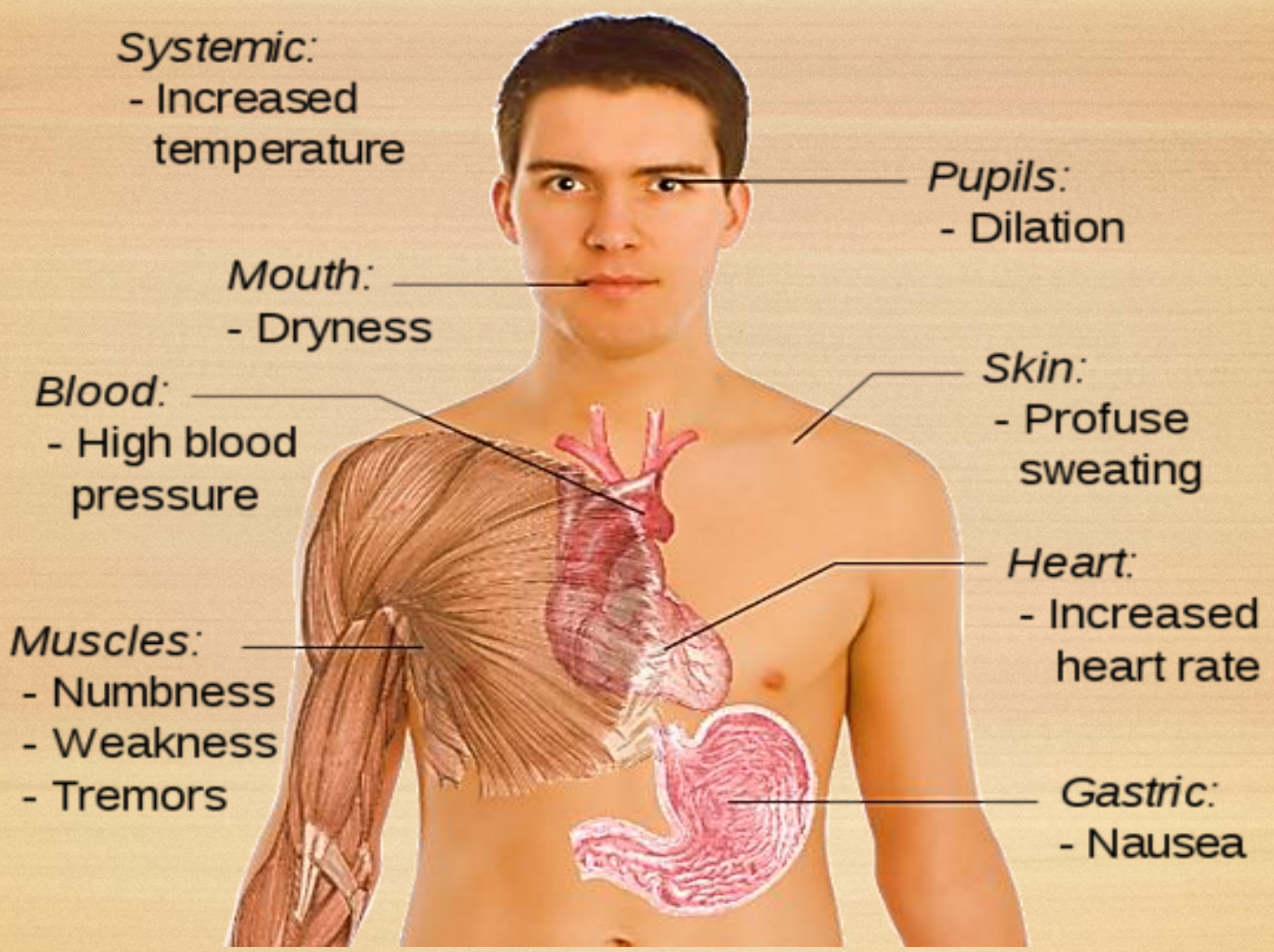
**(LSD)**

**Emotional effects**: Rapid shifts in mood from euphoria to depression from strength to weakness and panic emotions.

**Long-term effects**: Many users of LSD experience flashbacks (they re-experience the effects of the drug without any new dose being taken) The variety, intensity, and pattern of flashbacks are unpredictable and do not rely on dose or frequency of use

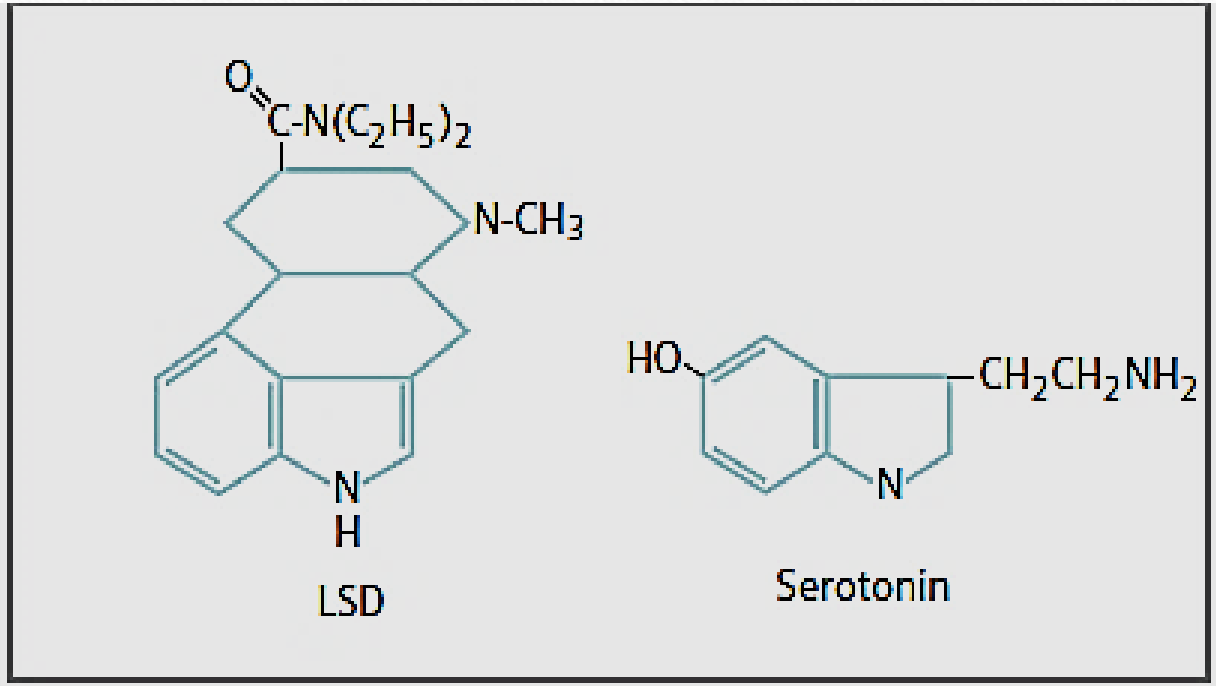
Physical effects of

# Lysergic acid diethylamide (LSD)



# LSD mechanism of Toxicity

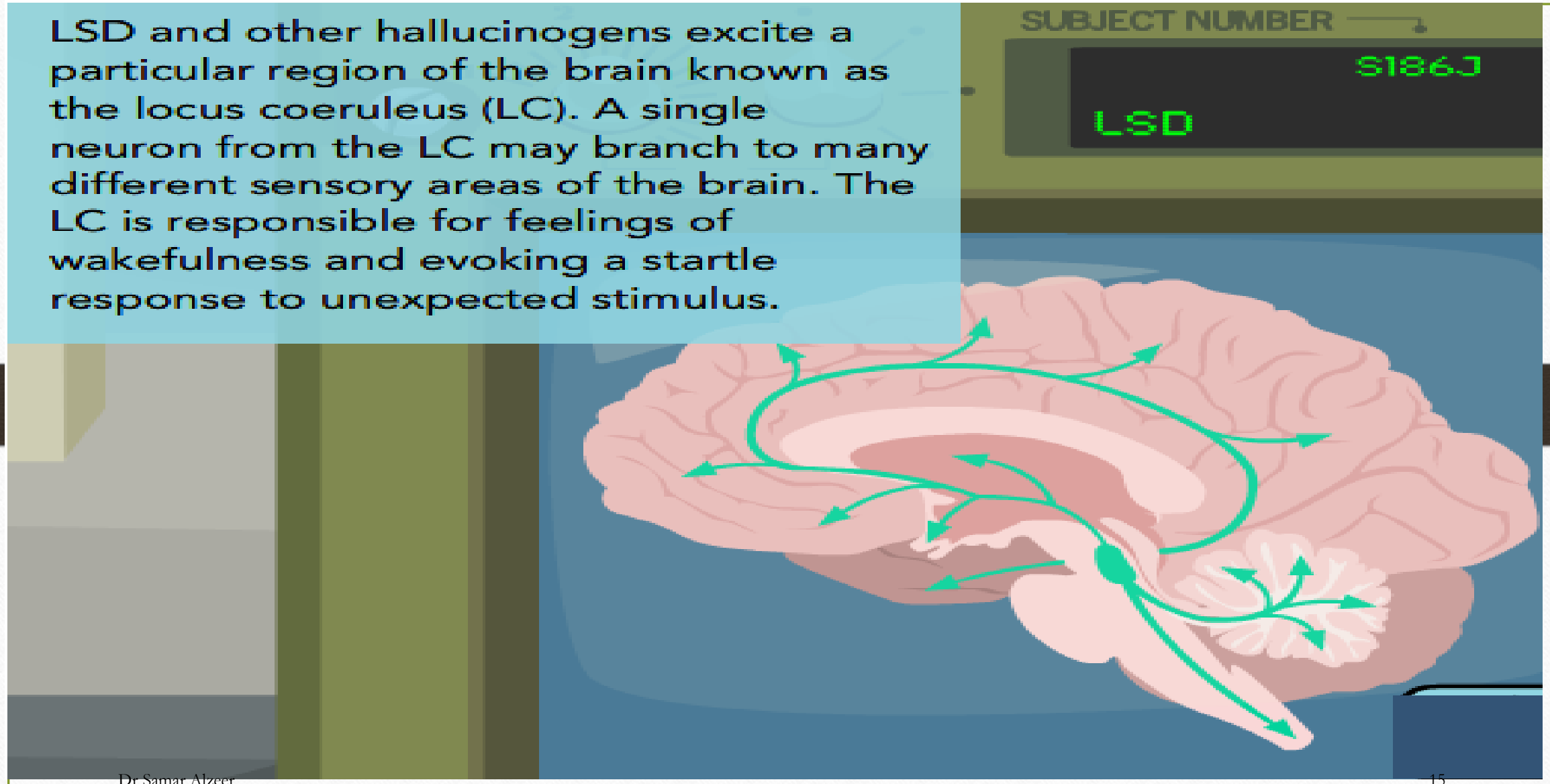
- Similar to serotonin
- LSD Binds to serotonin receptors (particularly 5-HT2)
- **Serotonin** : sleep / mood / appetite / memory
- Affect also dopamine receptors

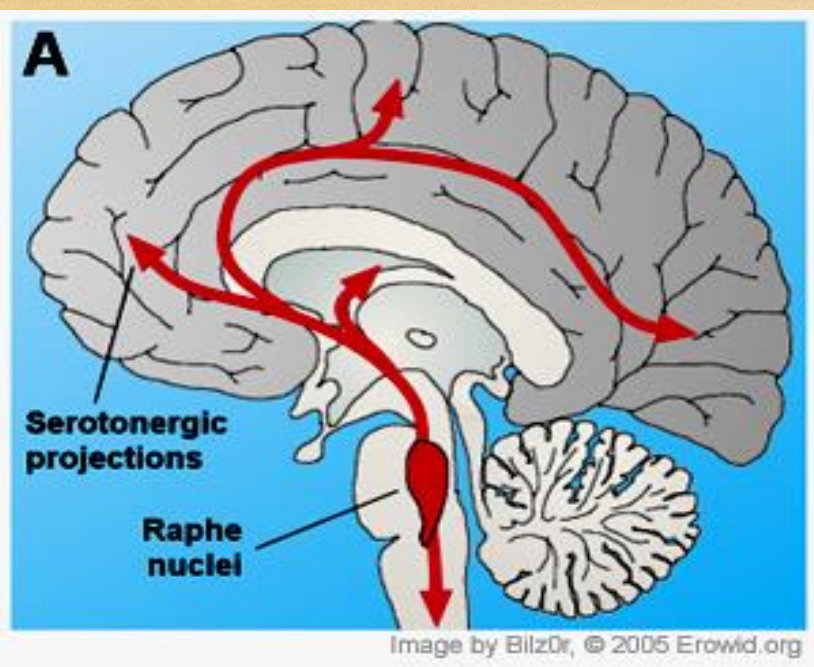


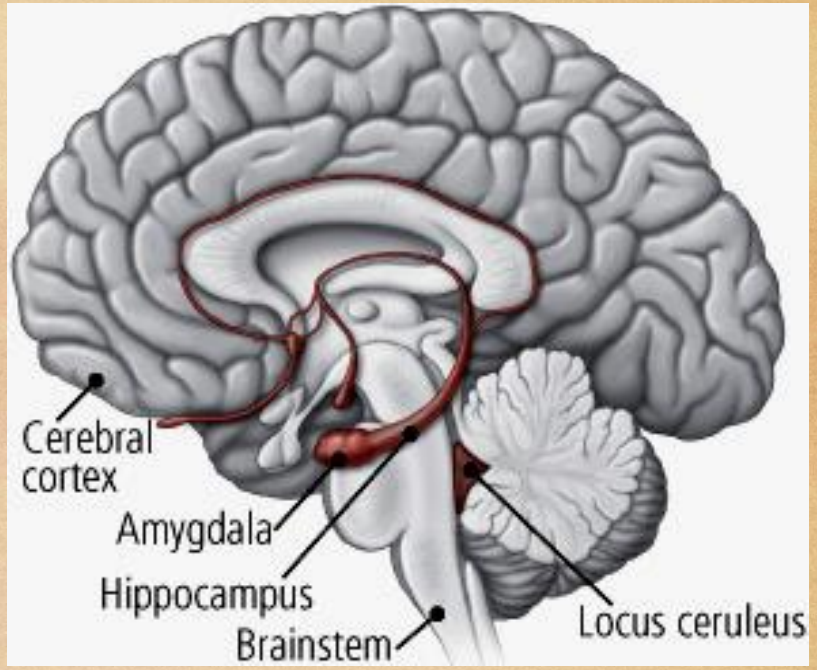
# LSD mechanism of Toxicity


LSD works on post-synaptic neuron

LSD and other hallucinogens excite a particular region of the brain known as the locus coeruleus (LC). A single neuron from the LC may branch to many different sensory areas of the brain. The LC is responsible for feelings of wakefulness and evoking a startle response to unexpected stimulus.

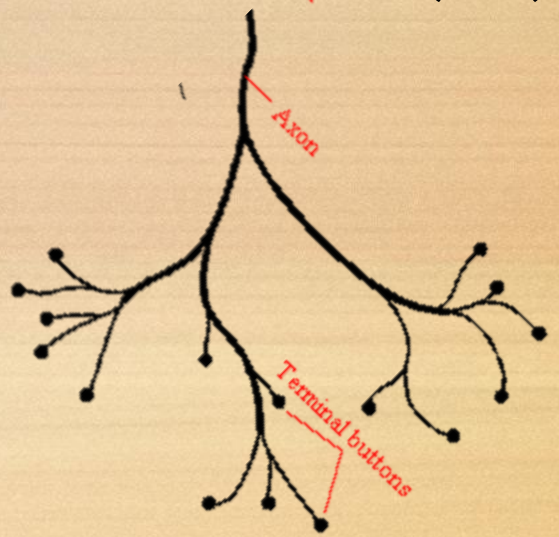





**Raphe Nuclei (RN)**

**Locus Ceruleus (LC)**




**LSD and other hallucinogenic drugs interact in one way or another with receptors located in the raphe nuclei and the locus coeruleus, which are the brain areas and targets for serotonin (5-HT) and noradrenaline (NA), respectively.**

# Toxicokinetics of LSD

Dose : 20-80 µg

10-20 min

For 8-12 hours

Food in the stomach slows absorption

**Cross BBB**

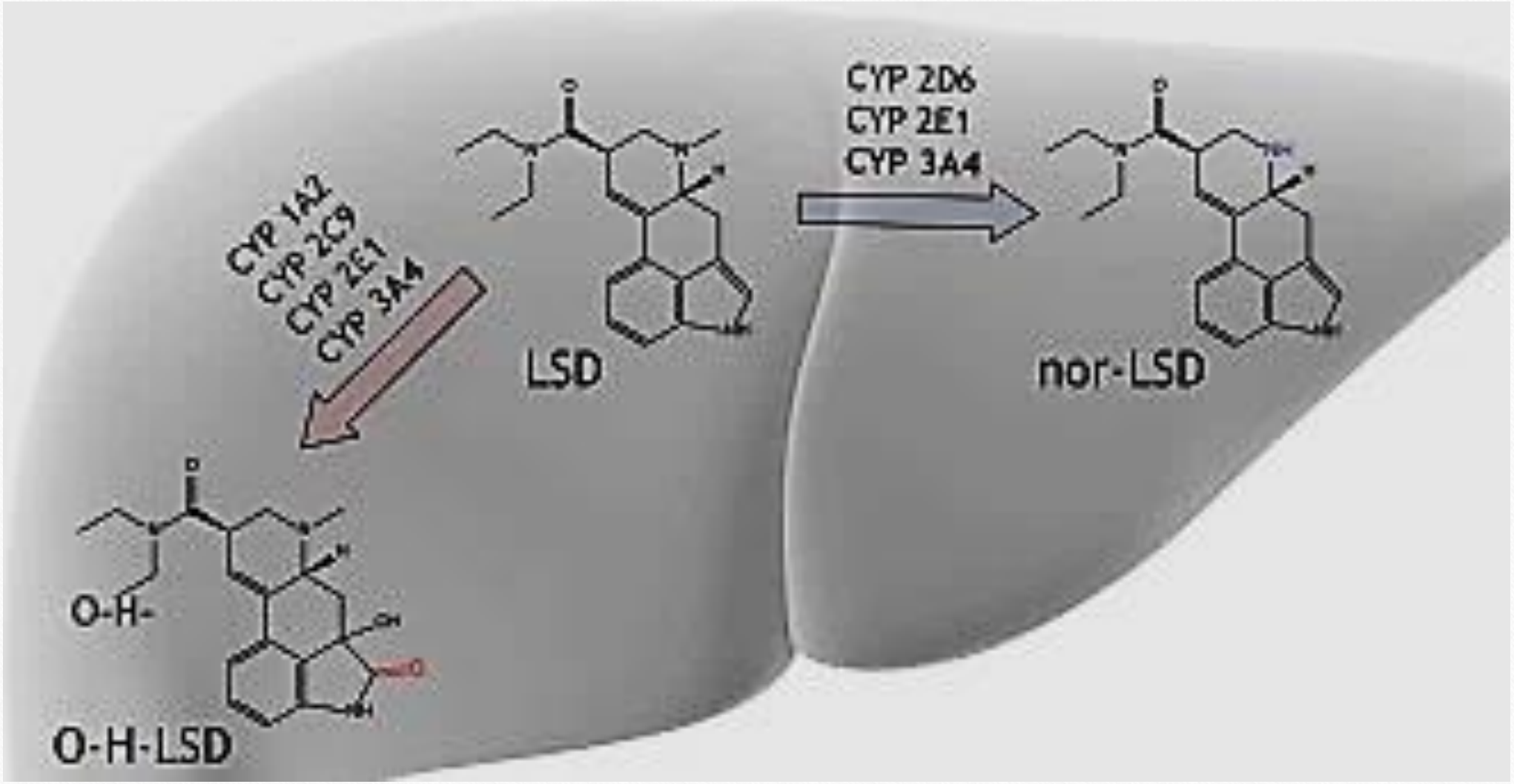
Protein binding: 80%

Brain , liver , spleen, lung

Metabolism

80% elimination in bile

T1/2 = 2.5-3 hours


CYP 1A2
CYP 2C9
CYP 2E1
CYP 3A4
CYP 2D6
CYP 2E1
CYP 3A4
LSD
nor-LSD
O-H-
O-H-LSD

# Detection of LSD

| Active compound | Detection window in blood | Detection window in urine |
|---|---|---|
| **LSD** | 6-12 hours | 24-80 hours |
| **O-H-LSD** | | 96 hours |

**Immunoassays**

**False-positive urine testing for LSD has been reported after exposure to several medications including fentanyl, sertraline, haloperidol, or verapamil**

HPLC/fluorescence detection and GC/MS for detection of LSD in urine

# Toxicity of LSD

Death from LSD is rare. No tolerance or withdrawal symptoms

Benzodiazepines are beneficial for sedation

Management of symptoms of sympathetic stimulation, especially tachycardia and hyperglycemia

No antidote

# Cannabis


Marijuana

Hashish

# Cannabis

## ❖ Marijuana

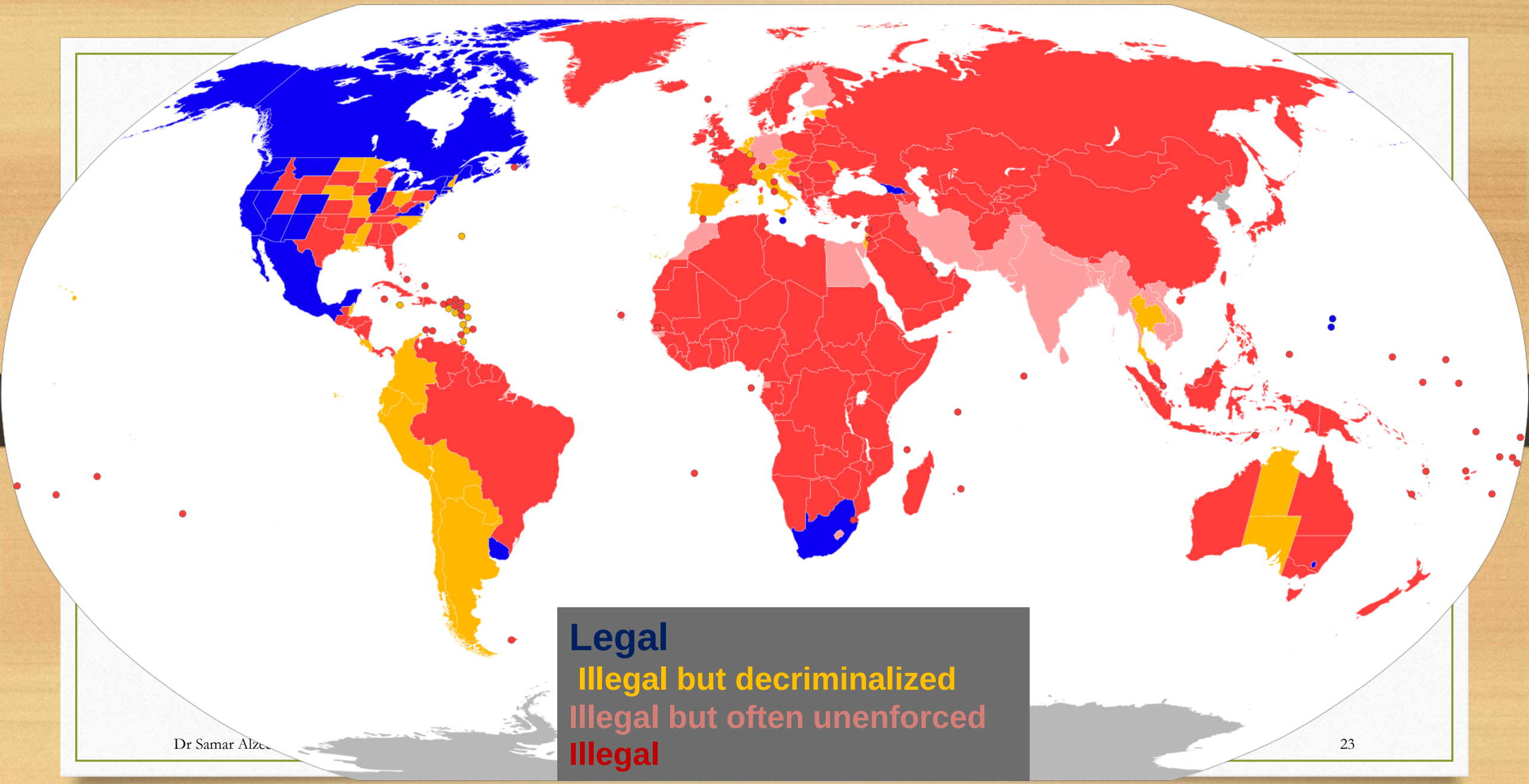
The leaves and flowering parts of the plant *Cannabis sativa*. 5 % of active component (cannabinoids)

## ❖ Hashish

Resin from the plant may be dried and compressed into blocks called hashish, 15 % of active component (cannabinoids)

## ❖ Hash oil

Extract of cannabis or cannabis resin and can contain up to 60% of active component (cannabinoids)


Legal
Illegal but decriminalized
Illegal but often unenforced
Illegal

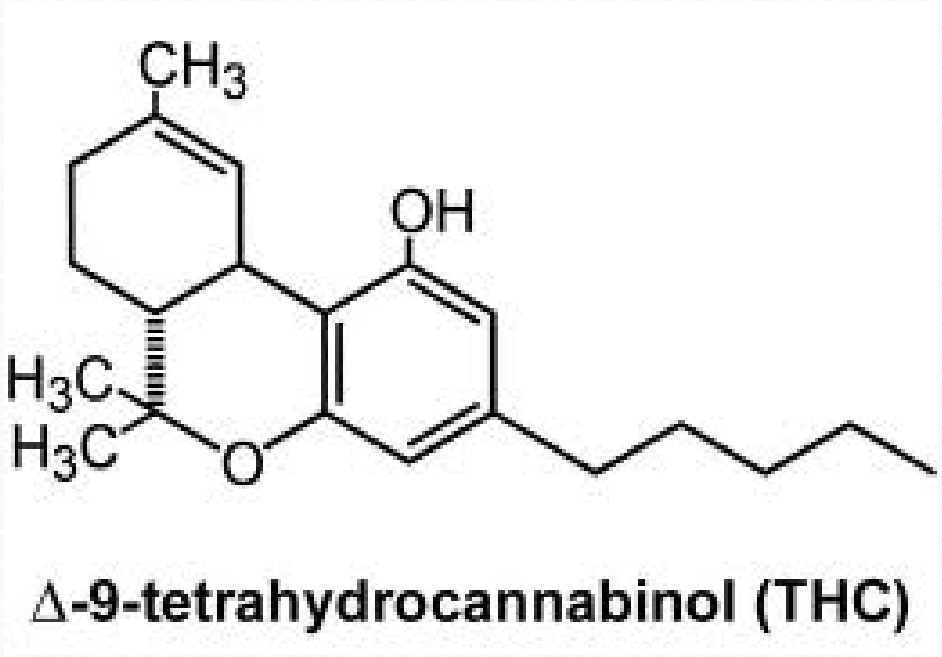
# Cannabis

- Cannabis sativa.L
- Oral or smoking

| UK | USA |
|---|---|
| B | Class I |

- 190 millions users around the world

# Cannabis




Δ-9-tetrahydrocannabinol (THC)

**THC**

Cannabinol (CBN)

cannabidiol (CBD)

Tetrahydrocannabivarol (THCV)

More than 20 metabolites

**Marijuana**
(Dried leaves and flowering heads)

**Hashish**
(Resin from upper leaves and flower buds)

**Isolated pure compounds**

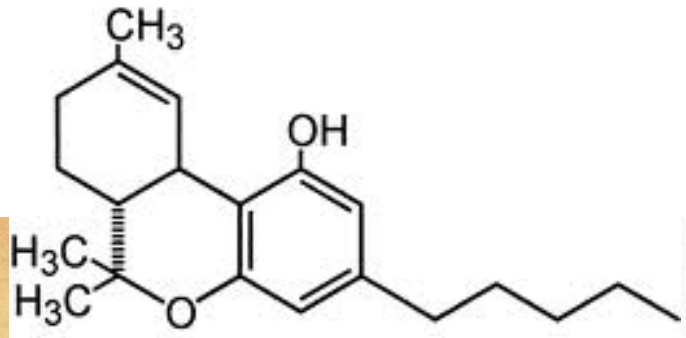
**Non –cannabinoids**

**Cannabinoids**

**Psychoactive**
$\Delta^9$-THC
$\Delta^8$-THC

**Active but not psychoactive**
Cannabidiol

**Inactive**
more than 60 compounds




Δ-9-tetrahydrocannabinol (THC)

**THC**

Cannabinol (CBN)

cannabidiol (CBD)

Tetrahydrocannabivarol (THCV)

More than 20 metabolites

# Medical uses of Cannabis

- **Appetite stimulant** for patients with such conditions as AIDS-related anorexia
- **Treatment for vomiting** associated with cancer chemotherapy cancer patients (tradename Dronabinol® or Marinol® )



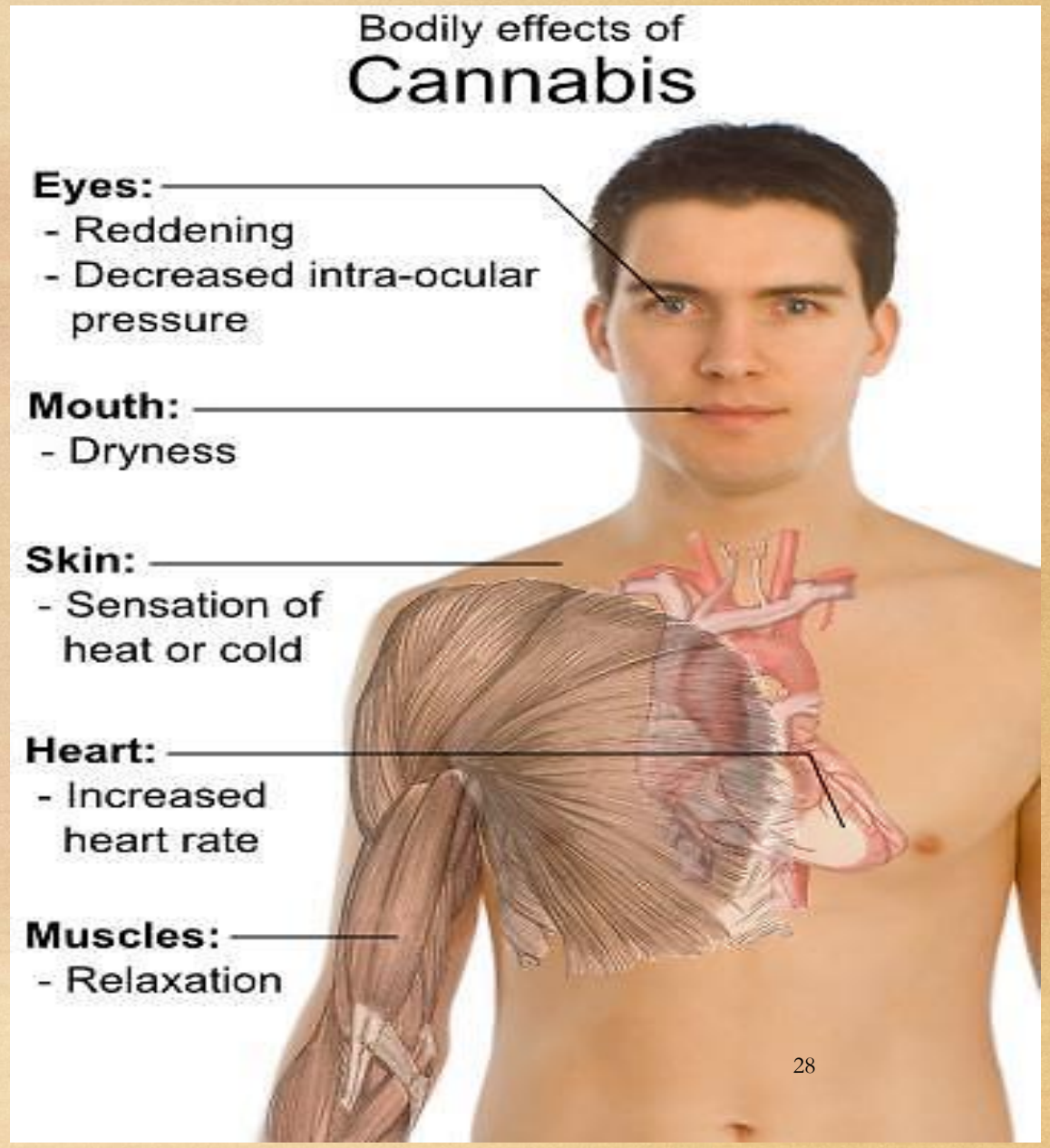
- **Decrease eye pressure (Treat Glaucoma): Canasol ®**


- **Chronic pain, multiple sclerosis**

# Desired & adverse effects

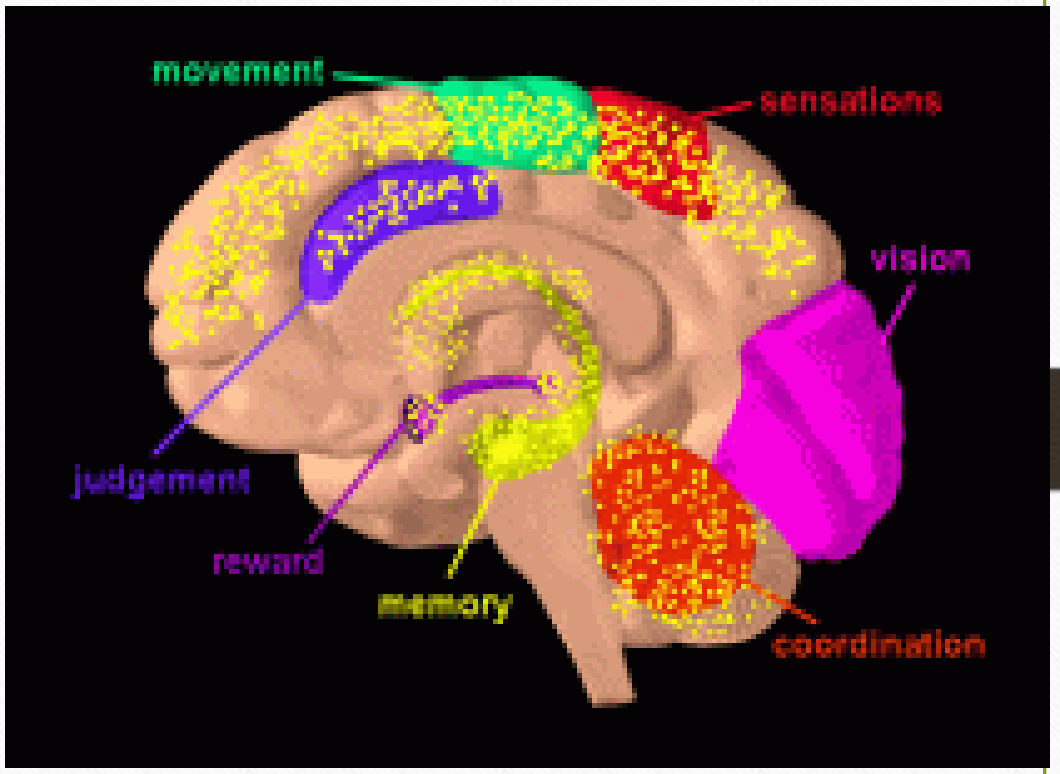
**Autonomic sympathetic-mediated symptoms**

- Dry mouth
- Stimulation of appetite,
- muscular incoordination
- decrease of testosterone levels
- urinary retention,
- increase in heart rate and
- Redness of eye (decreased intraocular pressure)
- Cannabinoid Hyperemesis Syndrome



# Desired effects

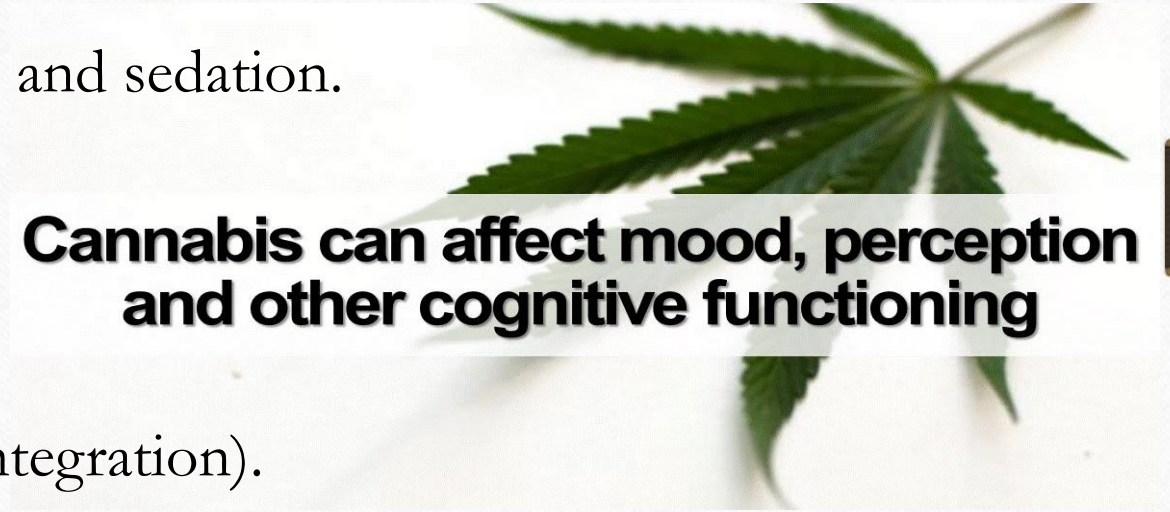
- Altered senses (for example, seeing brighter colors)
- Changed sense of time (temporal disintegration)
- Mood changes
- Weakness in body movement
- Difficulty thinking and problem solving and poor memory
- Hallucinations (when taken in high doses)
- Delusions (when taken in high doses)
- Psychosis (risks are higher with regular use of high potency marijuana)



# Desired & adverse effects

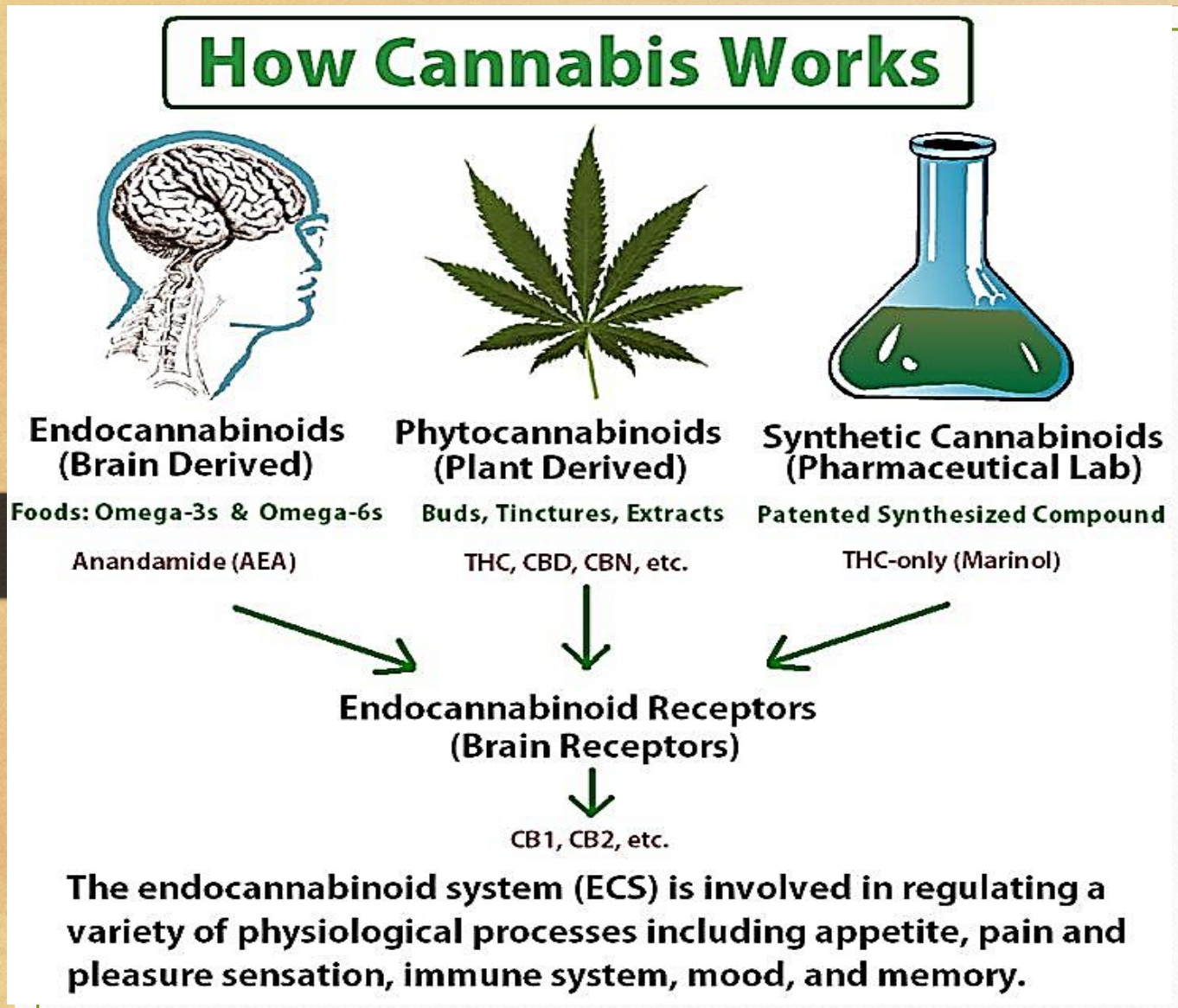
**Mood changes** :

- Euphoria, depression, paranoia, and anxiety to detachment.
- Most prominent effects are relaxation and sedation.




**Behavioural effects** :

- Loss of goal-oriented drive
- Loss of short-term memory
- A vague sense of time (temporal disintegration).

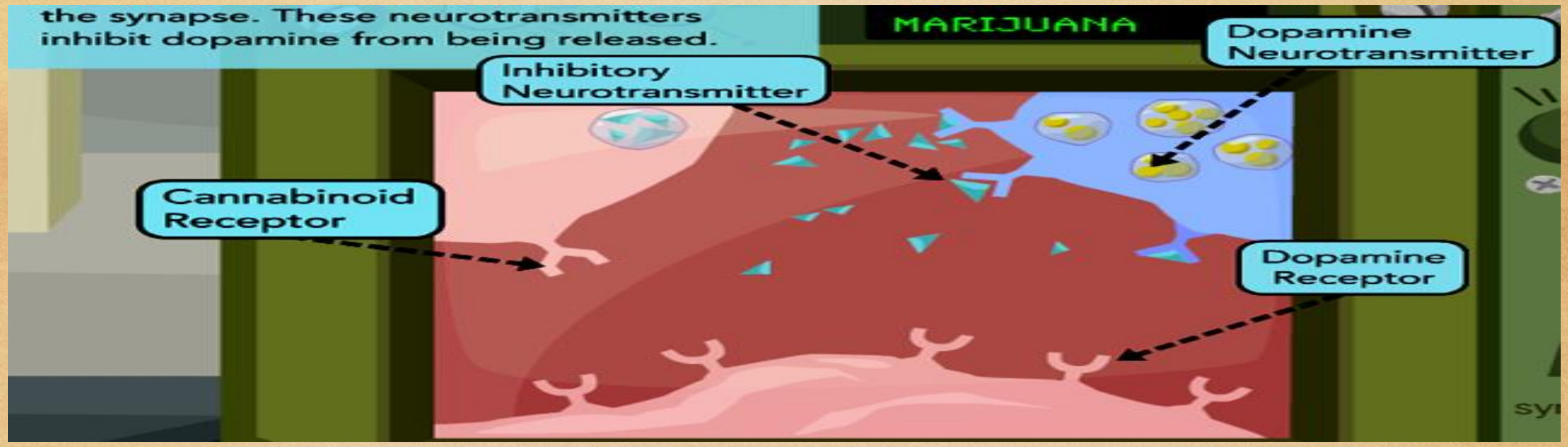



Anandamide is derived from arachidonic acid and binds to endogenous receptors CB1 and CB2

The CB1 receptor is mostly found in the brain, while the CB2 receptor is found in immune tissues such as the spleen, thymus, and tonsils, but not in the brain

# Mechanism of Toxicity

1

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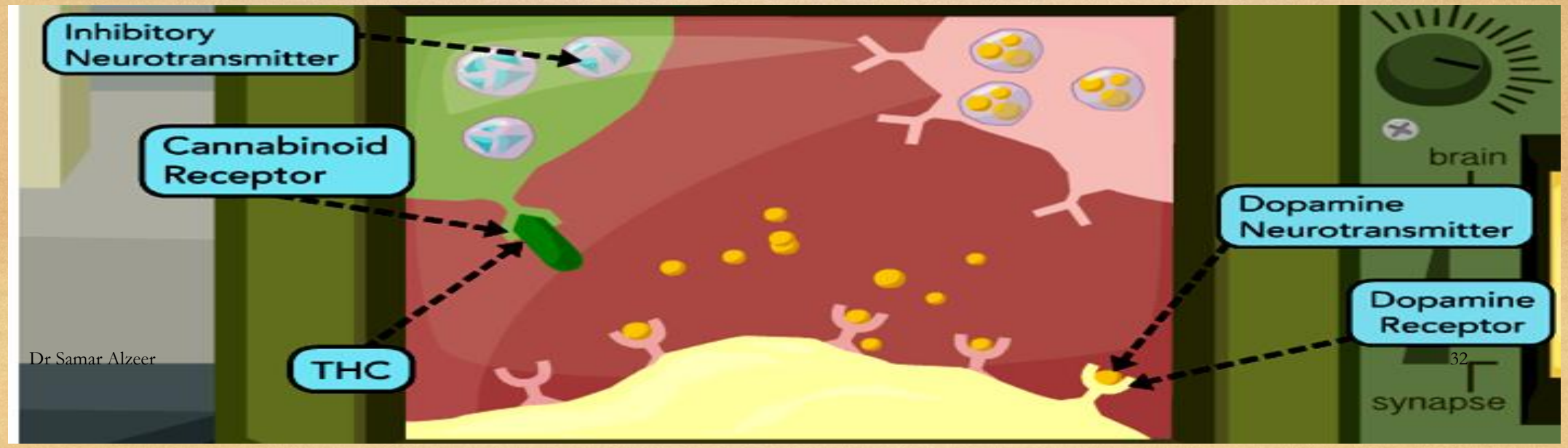
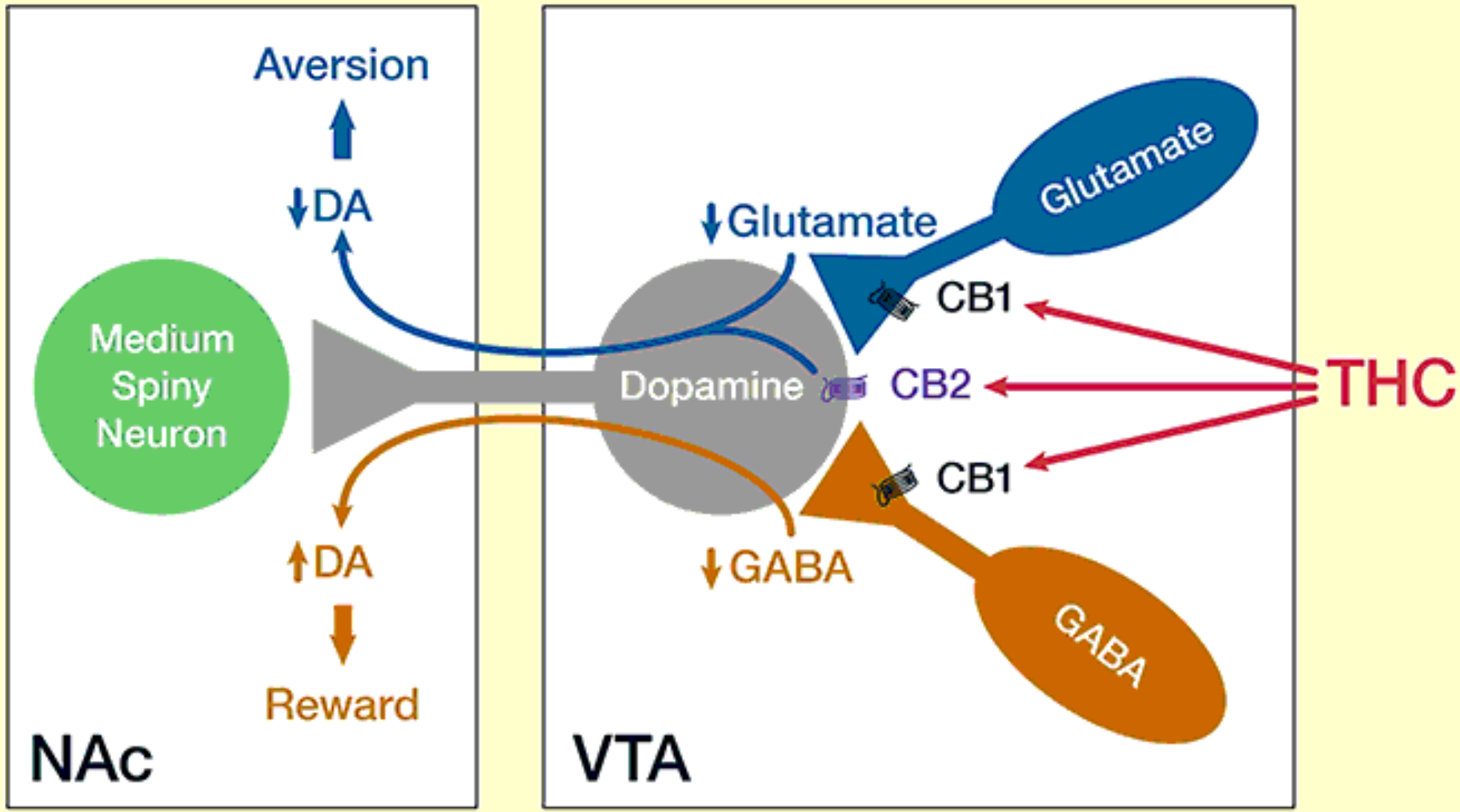
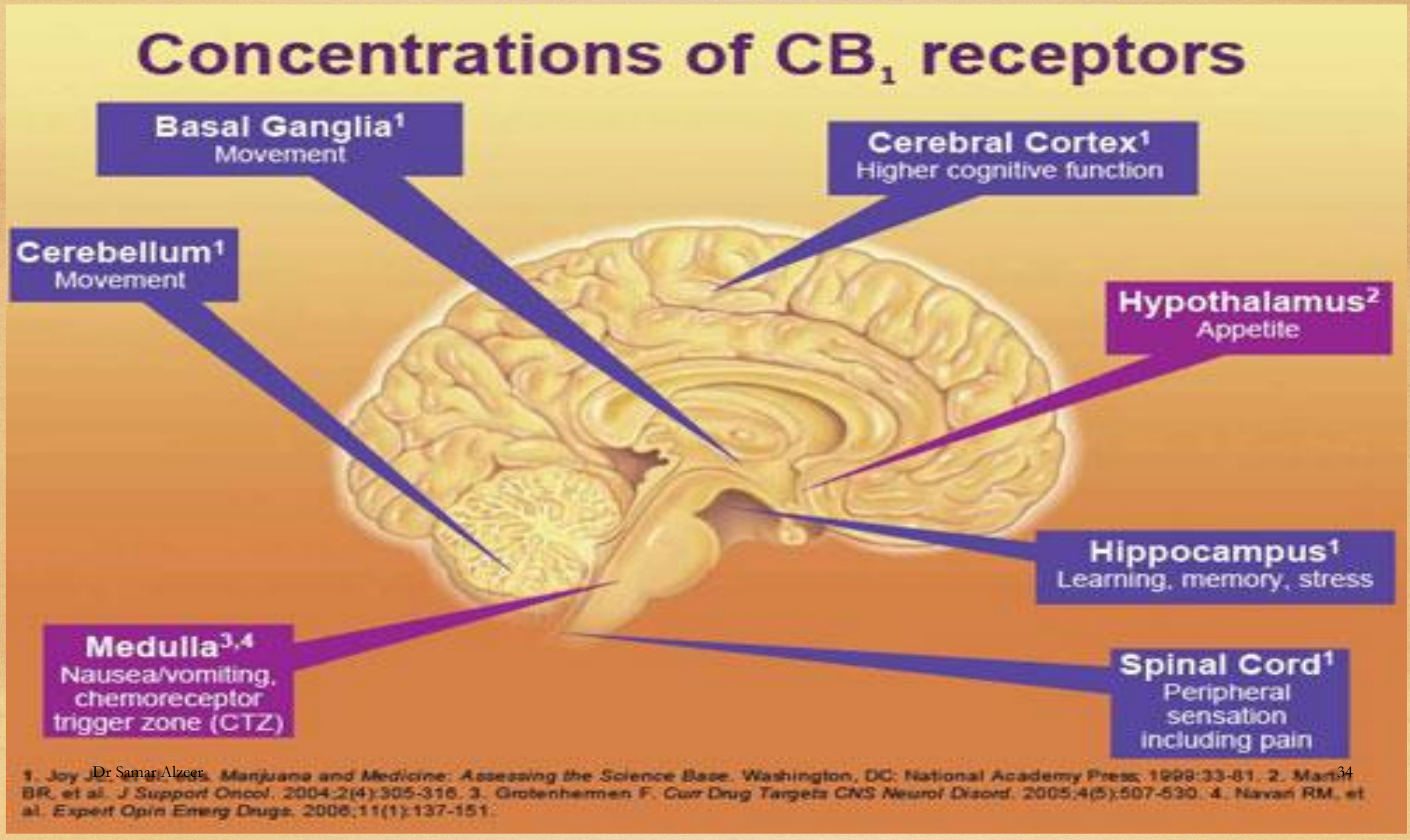





Adapted from Han et al. 2017; permission for use of data provided by Dr. Z.-X. Xi.

# Concentrations of $CB_1$ receptors




1. Joy JE, Watson SJ, Benson JA, *Marijuana and Medicine: Assessing the Science Base*. Washington, DC: National Academy Press; 1999:33-81. 2. Mantyh BR, et al. *J Support Oncol*. 2004;2(4):305-316. 3. Grotenhermen F. *Curr Drug Targets CNS Neurol Disord*. 2005;4(5):507-530. 4. Navari RM, et al. *Expert Opin Emerg Drugs*. 2006;11(1):137-151.

# Toxicokinetics of Cannabis

**Absorption**

- **Smoking**: rapid drug delivery (onset in 1-2 min, peak concentration in 3-8 min)
- **Oral**: Oral administration is almost completely absorbed (90%),onset in 0.5-1 hour . peak concentration in 2-4 hours

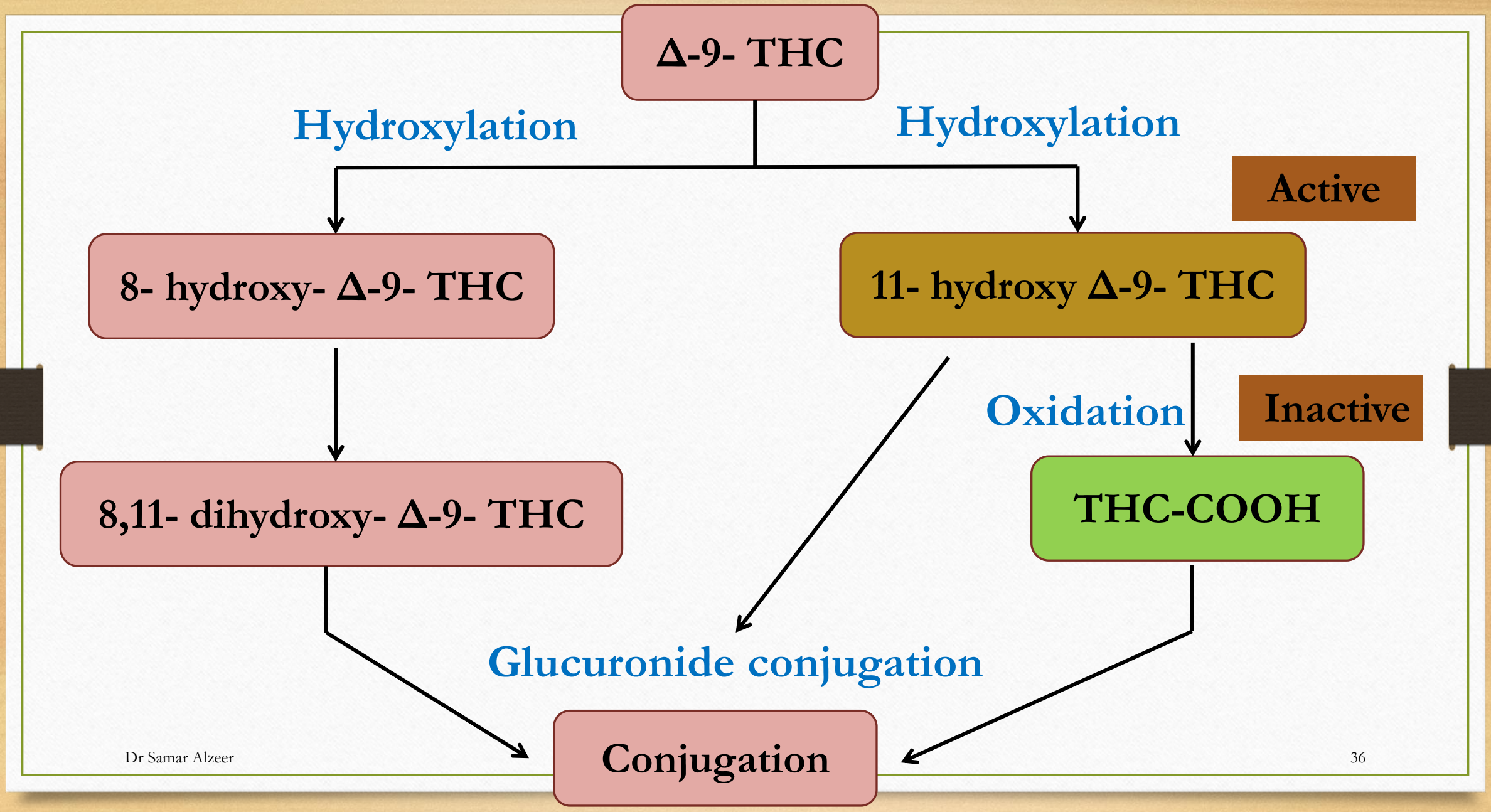
**Distribution**

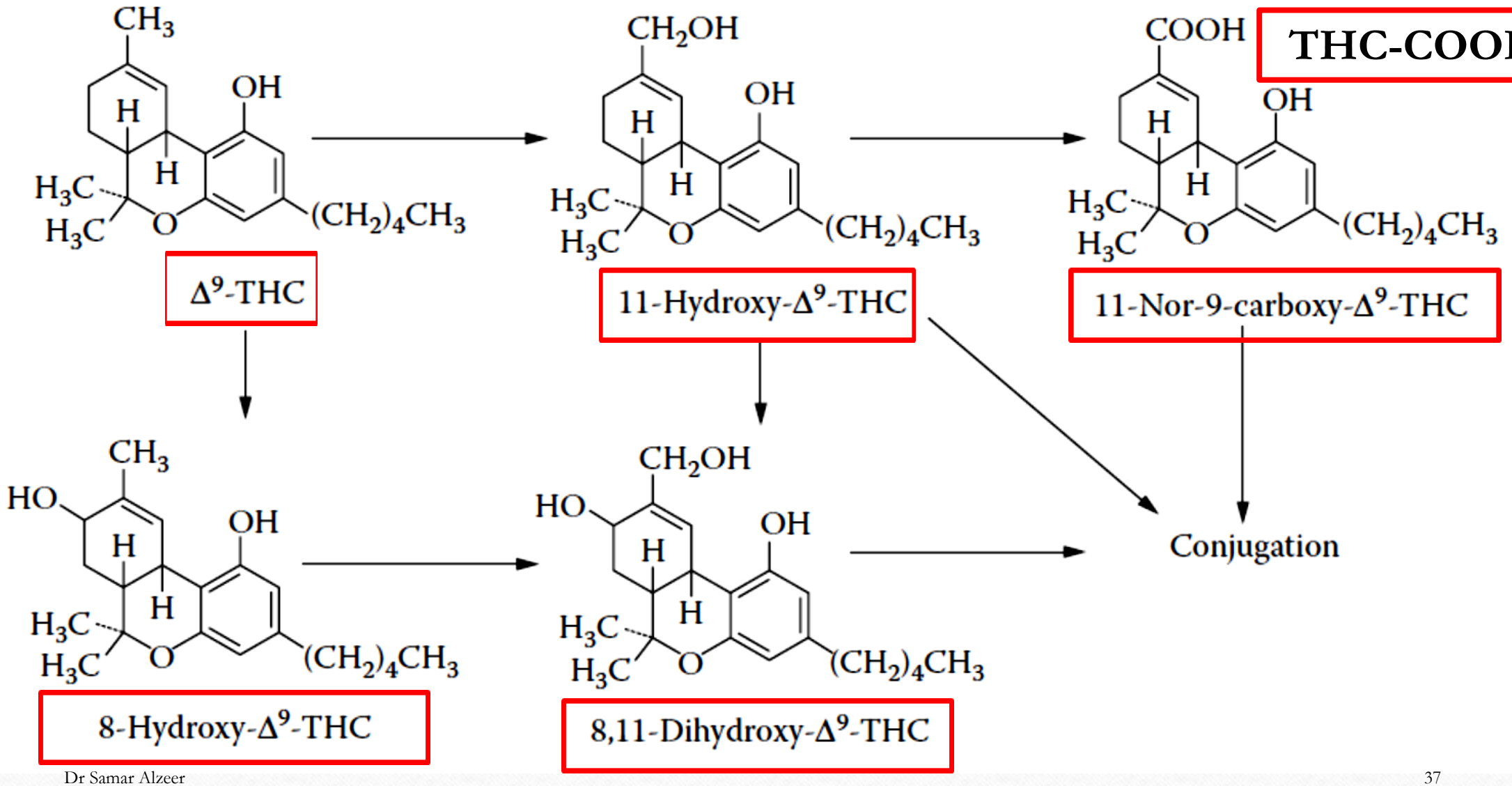
- **Protein binding** : 90-97%
- **Lipophilic**: large volume of distribution, biphasic pattern : brain, liver, heart, kidney, salivary glands, breast milk, fat, and lung

**Elimination**

Approximately 70% of a dose of THC is excreted in the urine (30%) and feces (40%) within 72 h

- **Elimination half-life = 1 day, can reach 7 days**


Δ-9- THC
Hydroxylation
Hydroxylation
Active
8- hydroxy- Δ-9- THC
11- hydroxy Δ-9- THC
Oxidation
Inactive
8,11- dihydroxy- Δ-9- THC
THC-COOH
Glucuronide conjugation
Conjugation


THC-COOH
Δ9-THC
11-Hydroxy-Δ9-THC
11-Nor-9-carboxy-Δ9-THC
8-Hydroxy-Δ9-THC
8,11-Dihydroxy-Δ9-THC
Conjugation

# Detection

| Active compound | Detection window in blood | Detection window in urine | Detection window in saliva |
|---|---|---|---|
| THC | 5 hrs | 10 hrs | 34 hrs |
| THC-COOH | 36 hrs | 2-7 days | |

| Usage | Detection Window in urine |
|---|---|
| One time | 3 days |
| Moderate use ( 4 times per week) | 5 days |
| Heavy use ( one time per day) | 10 days |
| Chronic heavy use | 30 days |

# Detection

Cannabinoids can be detected in plasma or urine. Enzyme-multiplied immunoassay technique (EMIT) and radioimmunoassay (RIA) are routinely available; gas chromatography-mass spectrometry (GC/MS) is the most specific assay and is used as the reference method.

**TABLE 83–2. Xenobiotics or Conditions Purported to Produce Inaccurate Screening Test Results for THC**

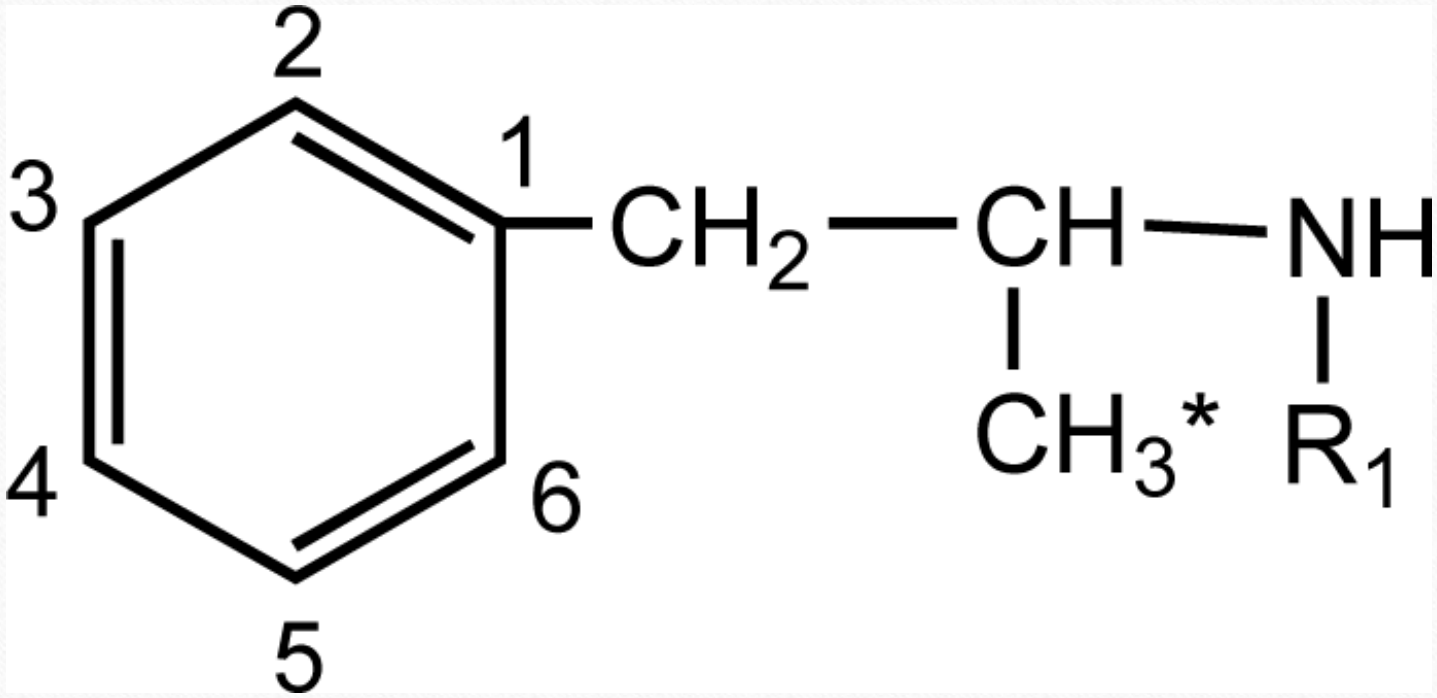
| False Negative[a] | False Positive |
|---|---|
| Bleach (NaOCl) | Dronabinol |
| Citric acid | Efavirenz |
| Detergent additives | Ethacrynic acid |
| Dettol[b] | Hemp seed oil |
| Dilution | NSAIDs |
| Glutaraldehyde | Promethazine |
| Lemon juice | Riboflavin |
| Potassium nitrite ($KNO_2$) | |
| Salt (NaCl) | |
| Tetrahydrozoline | |
| Vinegar (acetic acid) | |
| Water | |

**Immunoassays may give false-negative and false-positive test results**

# Toxicity of Cannabis

- Serious toxicity is uncommon
- Psychiatric reassurance and supportive care are adequate treatment modalities for acute toxicity
- No specific antidote
- Use benzodiazepines to treat psychological disturbances

# Phenethylamine Derivatives




- MDMA
- Mescaline
- DOM

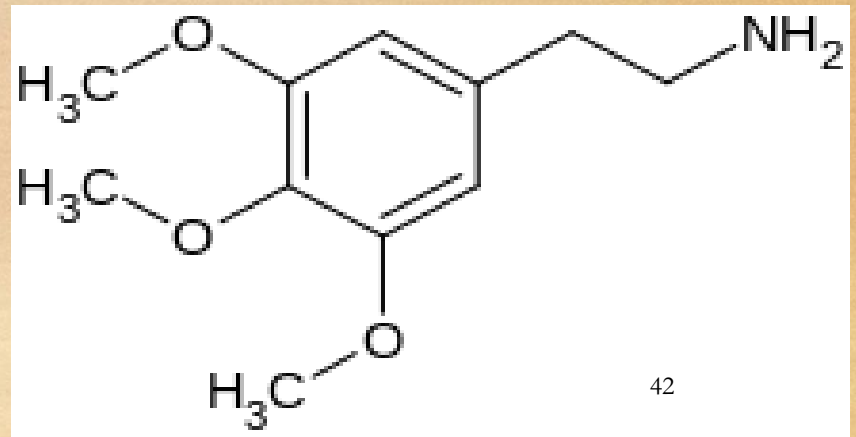
# Mescaline

- Mescaline is a natural drug , from Peyote Cactus (in USA and Maxico)

- It is derived from the dried tops of peyote buttons

- Mescaline was isolated and obtained in a pure form in 1896 by the German chemist Arthur Heffter

- Mescaline is 3,4,5-trimethoxy-phenylethylamine



# Mescaline

- The typical hallucinogenic dose of mescaline is about 200-400 mg or the equivalent of 10-20 grams of the dried peyote buttons
- Effects last about 12 hours
- Extracts from the buttons have a bitter taste, and make people vomit,

→ it is customary to prepare a tea by boiling the buttons or pods for several hours in water.

- Physiological effects are similar to LSD (hyperthermia, increase in heart rate, uncoordinated movements (ataxia), profound sweating, and flushing of the skin.

# Tryptamines Derivatives

## Psilocybin

- Natural drug, from magic mushrooms in South America, Mexico and USA.

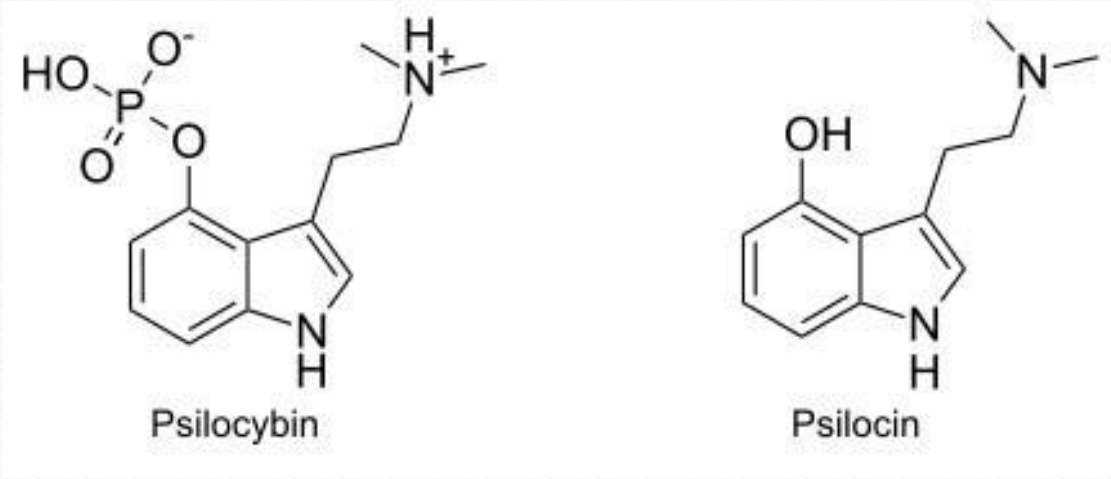
- Psilocybin is 4-phosphoryloxy-N,N-dimethyltryptamine

Psilocybin

# Psilocybin

- Psilocybin is converted into its active metabolite **psilocin**, which impairs autonomic functioning, causes behavioural changes, distorts awareness and alters perception

**Active metabolite**




- The principal target in the brain for LSD, peyote, and psilocybin are the nerve cells that use **serotonin** as the neurotransmitter for communication.

# Psilocybin

when eaten fresh or dried Mushrooms :

- Dilated pupils,
- People might vomit, become drowsy, people may hallucinate and experience distorted perceptions.

➢ First time users might suffer from **panic attacks**

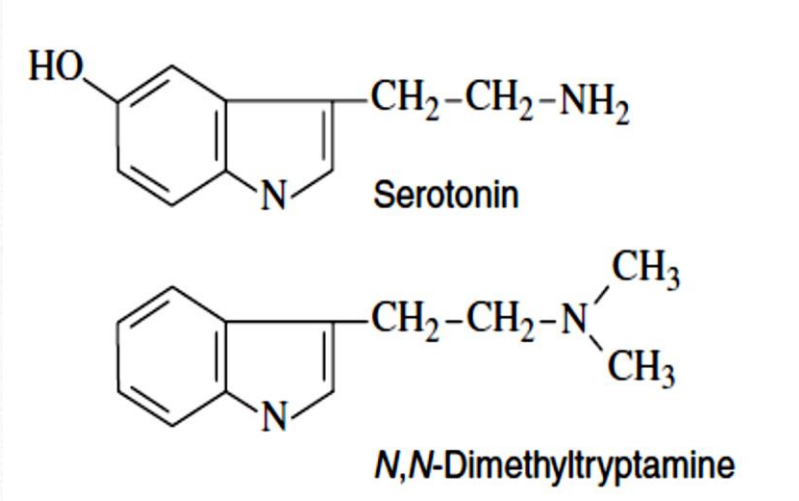
➢ **Flashbacks** are known to occur after chronic use

- Psilocybin is **heat stable** and can be brewed as a tea or added to other foods to mask the bitter alkaloid taste.

- Like LSD , Effects appears within 20 minutes and persist for approximately 6 hours

# N , N –Dimethyltryptamine (DMT)

- Blue elephant pill
- Of natural origin.
- Found in the bark of the Virola calophylla plant
- Found in the traditional drink of ayahuasca in South America
- It loses its effectiveness by hepatic metabolism, so it is combined with MAOI inhibitors to increase its oral effectiveness
- Effect on serotonin




# Anticholinergic hallucinogens

- Atropine
- Scopolamine

- **Anticholinergic drugs** include atropine, scopolamine, and hyoscyamine are competitive antagonists of acetylcholine muscarinic (M-) receptors that potently modulate the central nervous system (CNS).

- These drugs also evoke potent psychotropic effects, including characteristic delirium-like states with hallucinations, altered mood, and cognitive deficits.

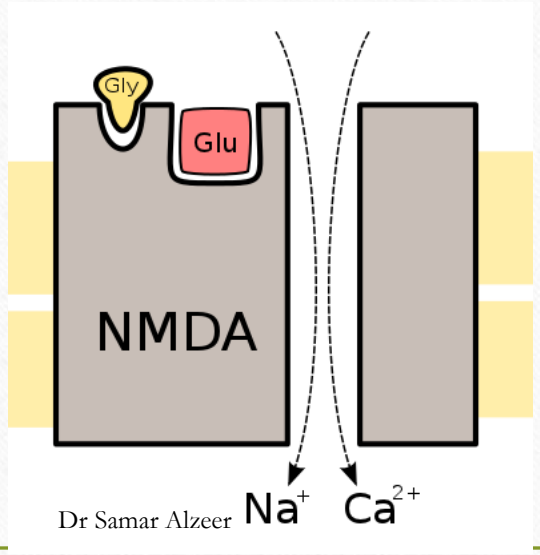
- State of delirium and confusion with hallucinations and complex visual imagery

# Dissociative Hallucinogens

**Dissociative Hallucinogens** :

- distort perceptions of sight and sound and
- produce feelings of detachment – dissociation – from the environment and self.

- Non competitive antagonist of NMDA receptor

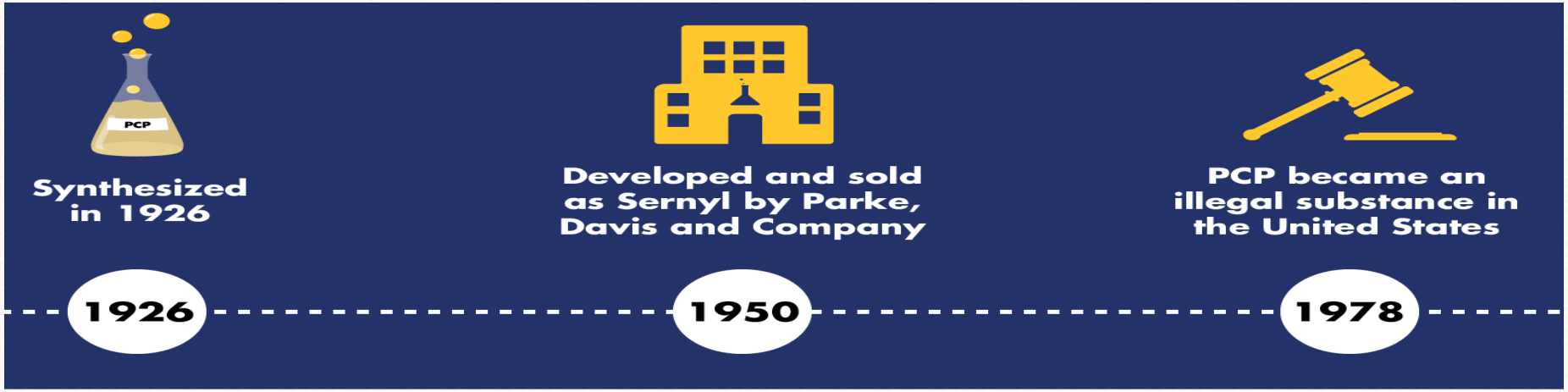


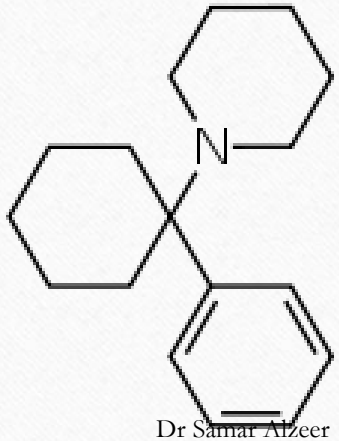

- Synthetic drugs

- PCP : schedule II (USA) , class A (UK)
- Ketamine : schedule III (USA) , class B (UK)

# Dissociative Hallucinogens

## Phencyclidine (PCP)

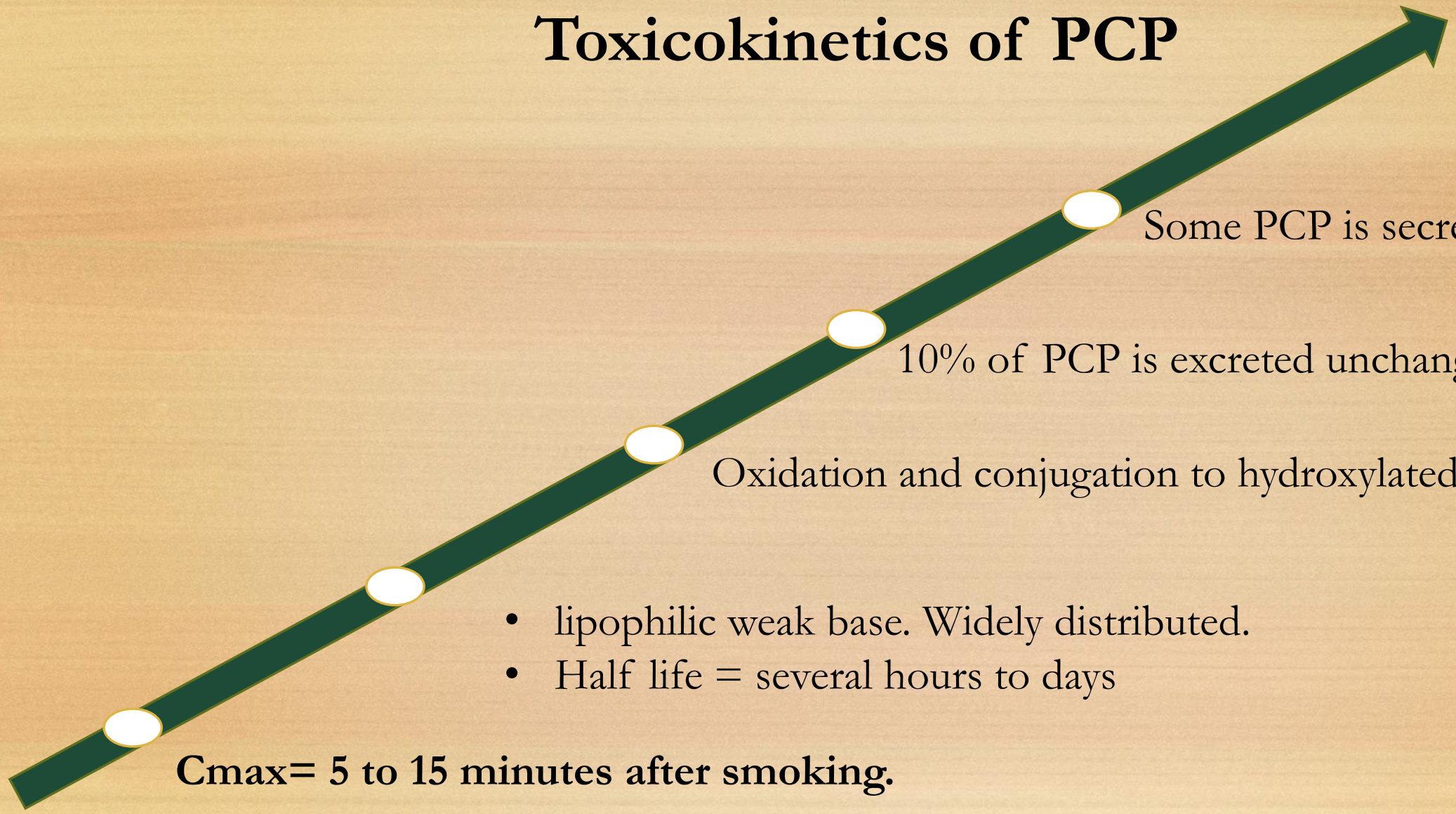


- **Medical use** : i.v. surgical anesthetic in the 1960s. It was banned
- Side-effects : postanesthetic confusion and delirium
- PCP is usually snorted or sprinkled on marijuana, tobacco and then smoked (inhalation route). Several hours effect

# Effects of PCP


# Toxicokinetics of PCP



Some PCP is secreted in the saliva

10% of PCP is excreted unchanged in the urine

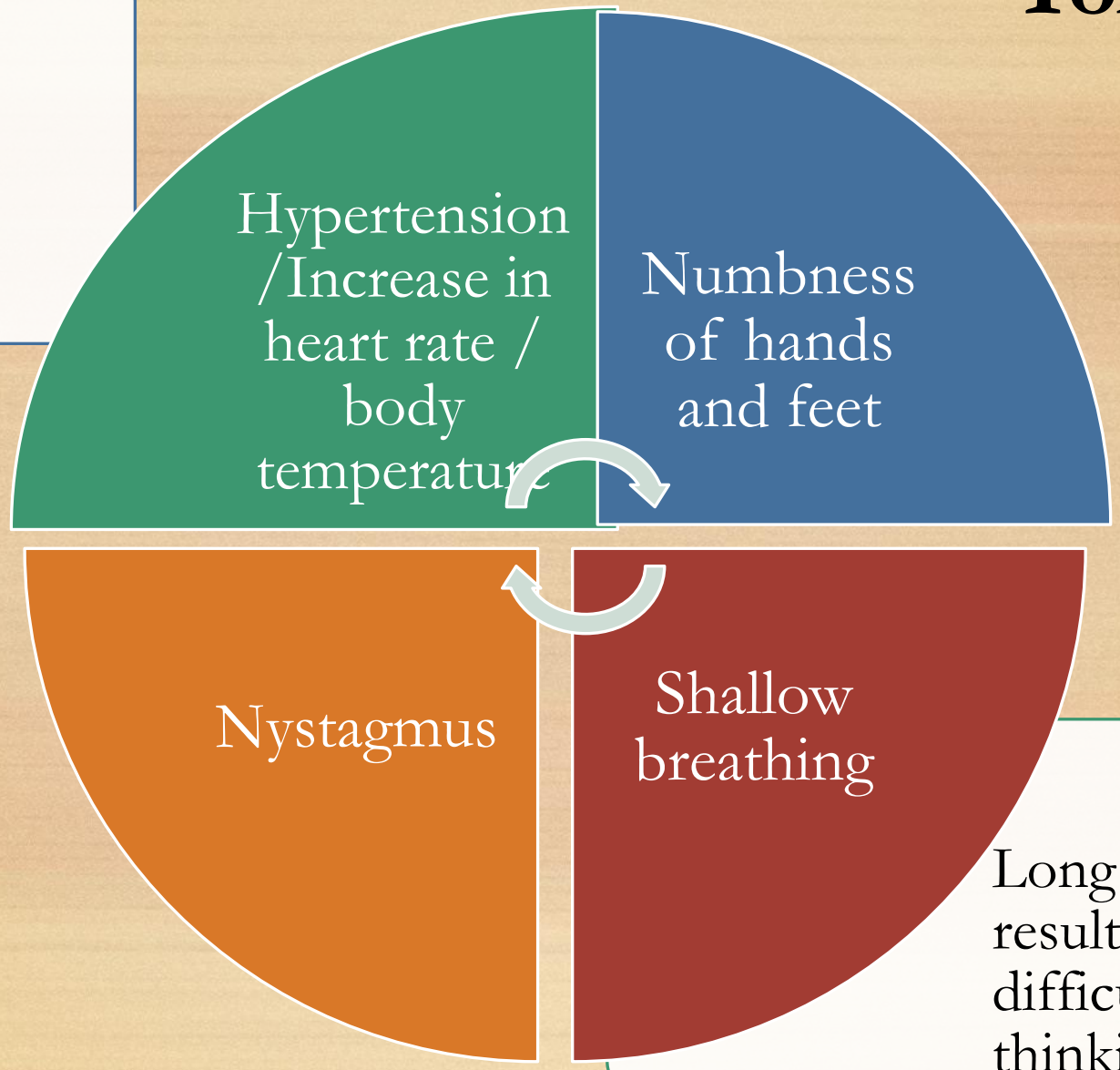
Oxidation and conjugation to hydroxylated metabolites

- lipophilic weak base. Widely distributed.
- Half life = several hours to days

**Cmax= 5 to 15 minutes after smoking.**

# Toxicity of PCP

- aggression and psychosis




Long term use of PCP results in memory loss, difficulties with speech thinking clearly

# Detection of PCP

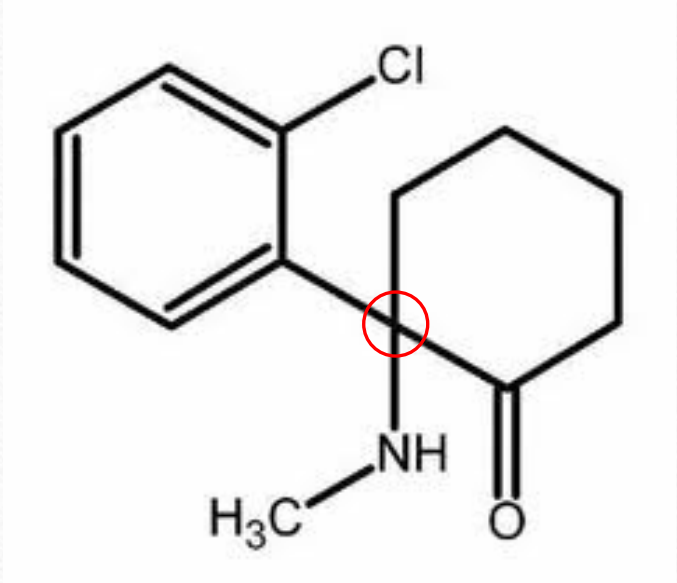
- Urine samples can remain positive for up to four weeks after ingestion in chronic users.
- ELISA and RIA are the methods of choice for urine drug toxicology screening
- Methods for confirmation include gas-liquid chromatography with nitrogen-phosphorus detection (GLC/NPD) or GC/MS.
- Other drugs, such as thioridazine, dextromethorphan, and chlorpromazine, may show false-positive reactions in immunochemical assays for PCP

# Ketamine

- In the 1960s
- Used in the Vietnam war , and as a veterinary anesthetic
- Substitute to PCP
- Able to cross BBB

- Oral (tablets or syrup)
- Inhaler , injection
- R ketamine more powerful than S ketamine

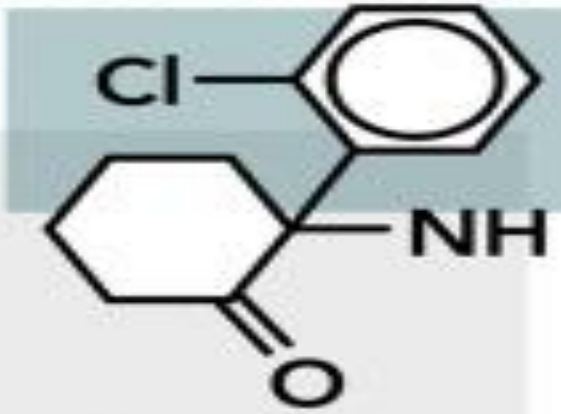
- Vitamin K , K , Special K, Black hole




- Hypnotic
- Analgesic
- amnesic

# uses of ketamine

## POSSIBLE:




addiction treatment

asthma treatment (questionable)

pain management

acute chronic

cancer-associated (questionable)

cancer suppression

## CURRENT:

veterinary anesthesia

field and ER anesthesia in adult humans

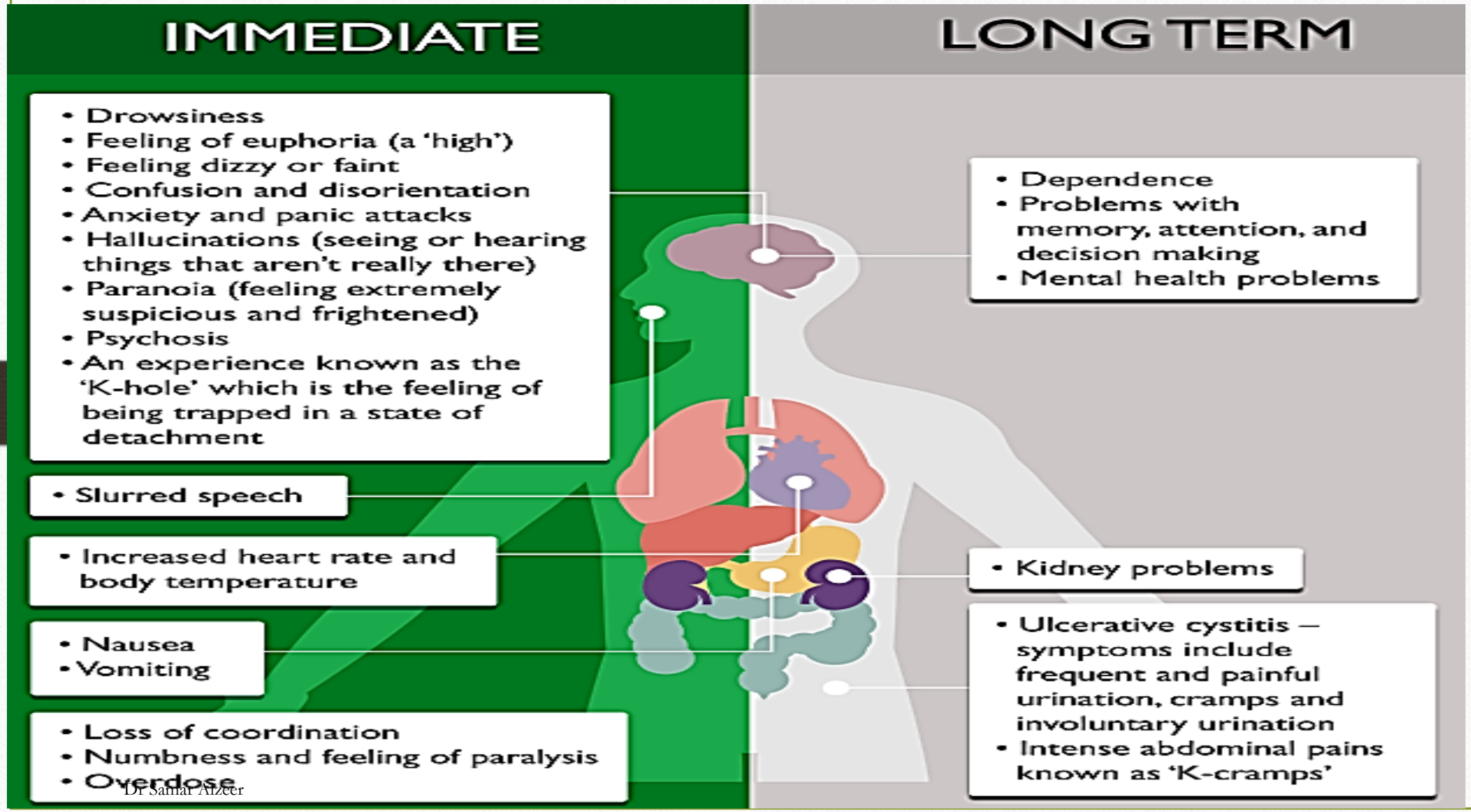
pediatric anesthesia

recreational drug

depression treatment

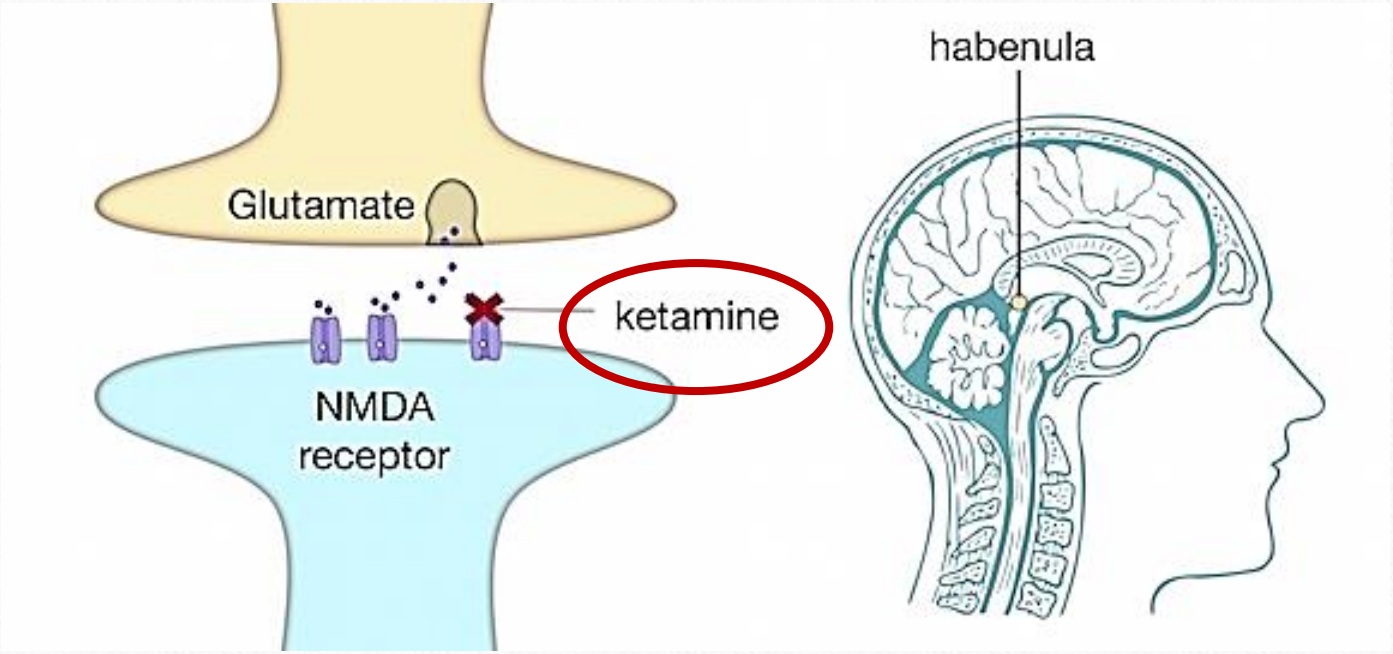
animal model of schizophrenia

# Ketamine


IMMEDIATE
LONG TERM
• Drowsiness
• Feeling of euphoria (a 'high')
• Feeling dizzy or faint
• Confusion and disorientation
• Anxiety and panic attacks
• Hallucinations (seeing or hearing things that aren't really there)
• Paranoia (feeling extremely suspicious and frightened)
• Psychosis
• An experience known as the 'K-hole' which is the feeling of being trapped in a state of detachment
• Dependence
• Problems with memory, attention, and decision making
• Mental health problems
• Slurred speech
• Increased heart rate and body temperature
• Kidney problems
• Nausea
• Vomiting
• Ulcerative cystitis — symptoms include frequent and painful urination, cramps and involuntary urination
• Intense abdominal pains known as 'K-cramps'
• Loss of coordination
• Numbness and feeling of paralysis
• Overdose

# Ketamine is non competitive antagonist of NMDA receptors

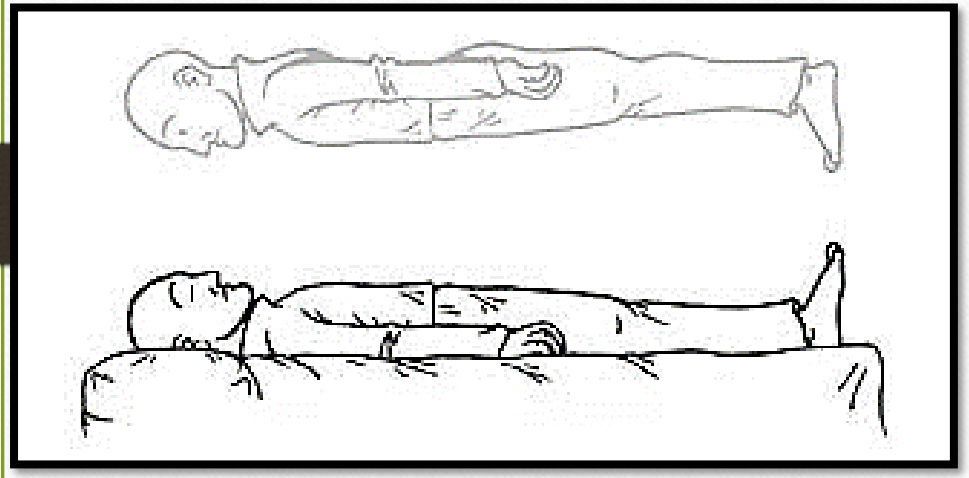
- Memory
- Learning




- Stop $Na^{+2}$ and $Ca^{+2}$ entrance into the cell and $K^{+}$ outside of the cell
- Some opioid receptor activity and sympathomimetic properties

# Near death experience

# Out of body experience



- **Dissociative : eyes are open during surgery**

## Adverse effects

- Hypertension
- Increase in heart rate
- Depression of respiratory system

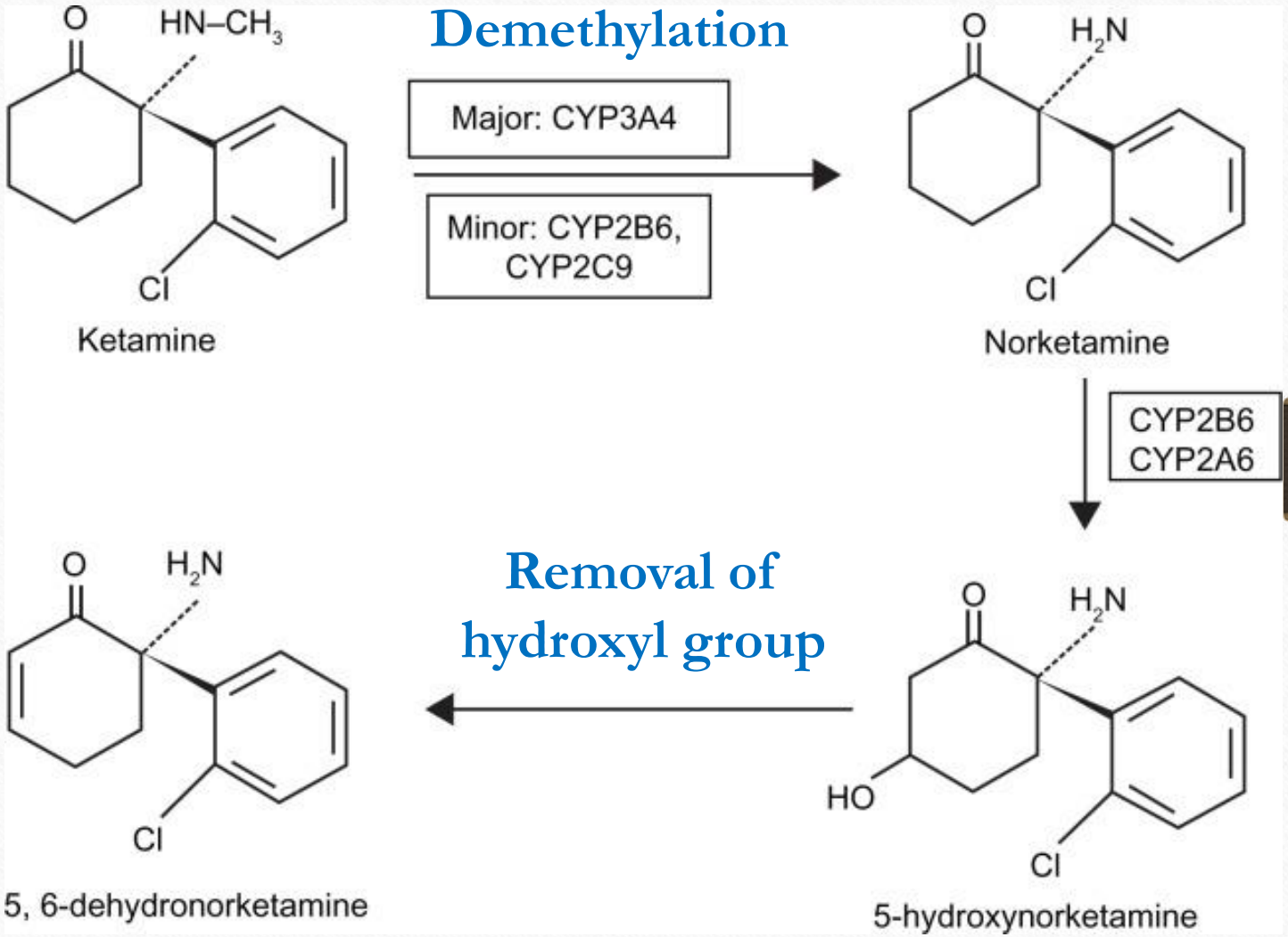
## Desired use

- Ecstasy
- Out of body experience
- DFSA

# Metabolism of ketamine

2 % of dose is eliminated unchanged in urine

T ½ = 2-3 hours



# Management of Toxicity

- Isolation from sensory stimuli
- IV benzodiazepines (diazepam) for seizure, and haloperidol for agitation,
- Severe hypertension is treated with nonspecific b-receptor antagonists (b-blockers), such as propranolol


- Behavioural psychiatric intervention is necessary for treatment of PCP drug addiction

# Forensic Toxicology

# DRUGS OF ABUSE –4– NARCOTICS

1

**Dr Samar Alzeer**

# Opiates and Opioids

peptide compounds
Derived from Morphine

Any nonpeptide agent binds at the opiate receptor site

| Natural | Semi-synthetic | Synthetic |
|---|---|---|
| Morphine | Heroin | Methadone |
| Codeine | Oxymorphone | Meperidine |
| | Hydromorphone | Pentazocine |
| | Oxycodone | Fentanyl |
| | Hydrocodone | |

- Most of them are prescription medications (severe pain relief, cough treatment, anti-diarrheal, addiction treatment)
- Prohibited opiates (heroin)

# THE OPIOID EPIDEMIC BY THE NUMBERS

**70,630**
people died from drug overdose in 2019[2]

**10.1 million**
people misused prescription opioids in the past year[1]

**1.6 million**
people had an opioid use disorder in the past year[1]

**2 million**
people used methamphetamine in the past year[1]

**745,000**
people used heroin in the past year[1]

**50,000**
people used heroin for the first time[1]

**1.6 million**
people misused prescription pain relievers for the first time[1]

**14,480**
deaths attributed to overdosing on heroin (in 12-month period ending June 2020)[3]

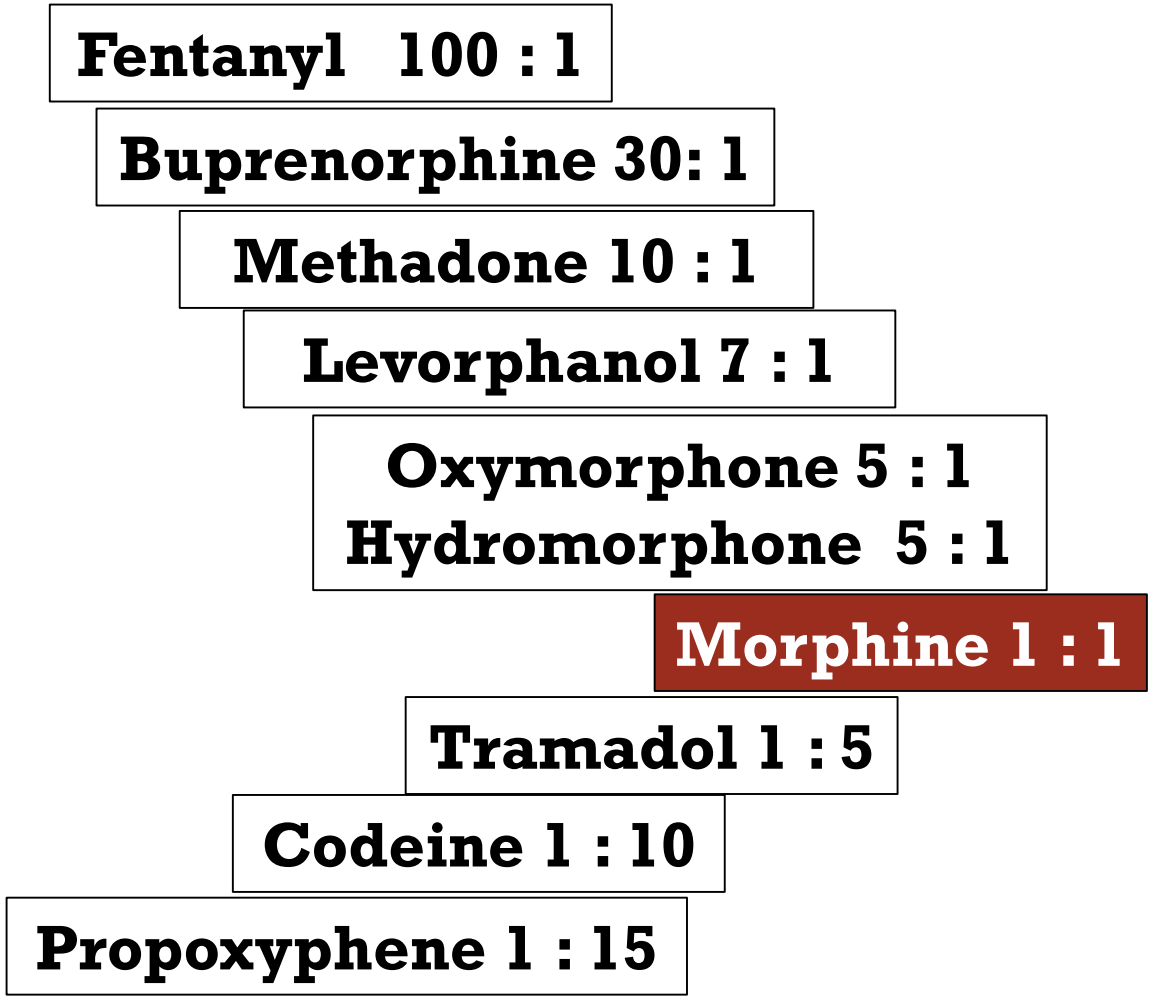
**48,006**
deaths attributed to overdosing on synthetic opioids other than methadone (in 12-month period ending June 2020)[3]

**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.


HHS.GOV/OPIOIDS

# Opioids Classification



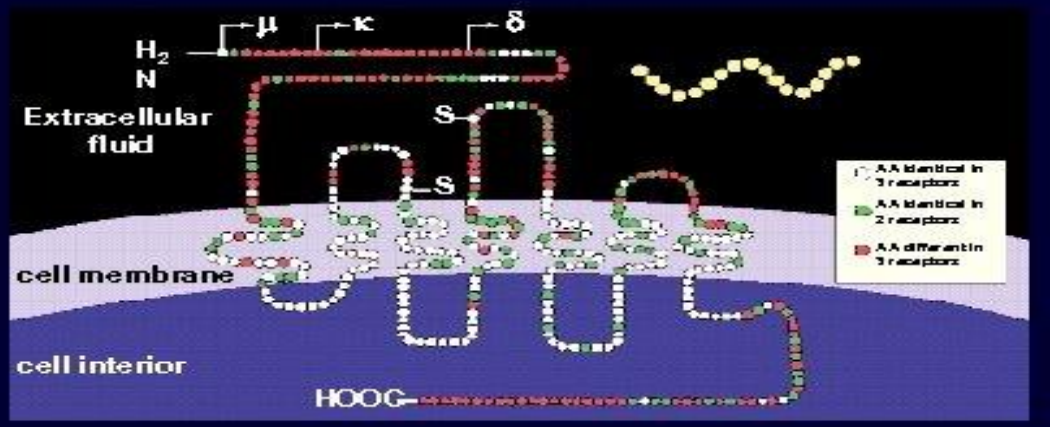

| USA | Drug |
|---|---|
| Schedule II | Morphine |
| Schedule III | Codeine |
| Schedule I | Heroin |
| Schedule II | Hydrocodone |
| Schedule II | Hydromorphone |
| Schedule II | Oxocodone |
| Schedule II | Oxomorphone |
| Schedule II | Methadone |

# Mechanism of Toxicity

Opioid receptors are: (Mu), (K), (Δ) to which natural opiates such as endorphins bind

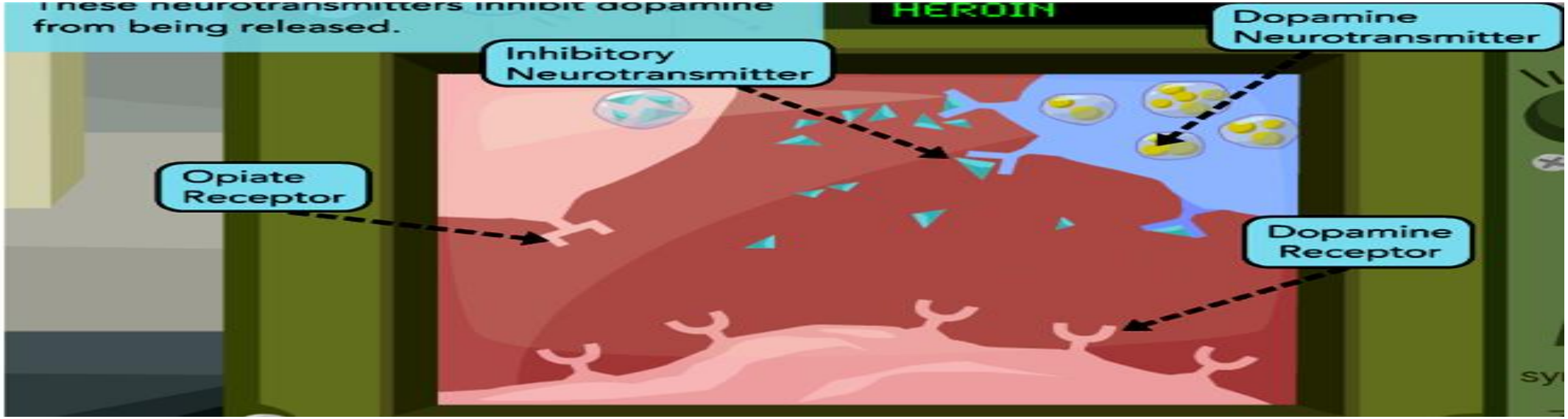
## Endogenous Opioids and their Receptors

| Opioid Classes | Opioid Receptor Types |
|---|---|
| Endorphins | Mu |
| Enkephalins | Delta |
| Dynorphins | Kappa |
| Endomorphins (?) | |

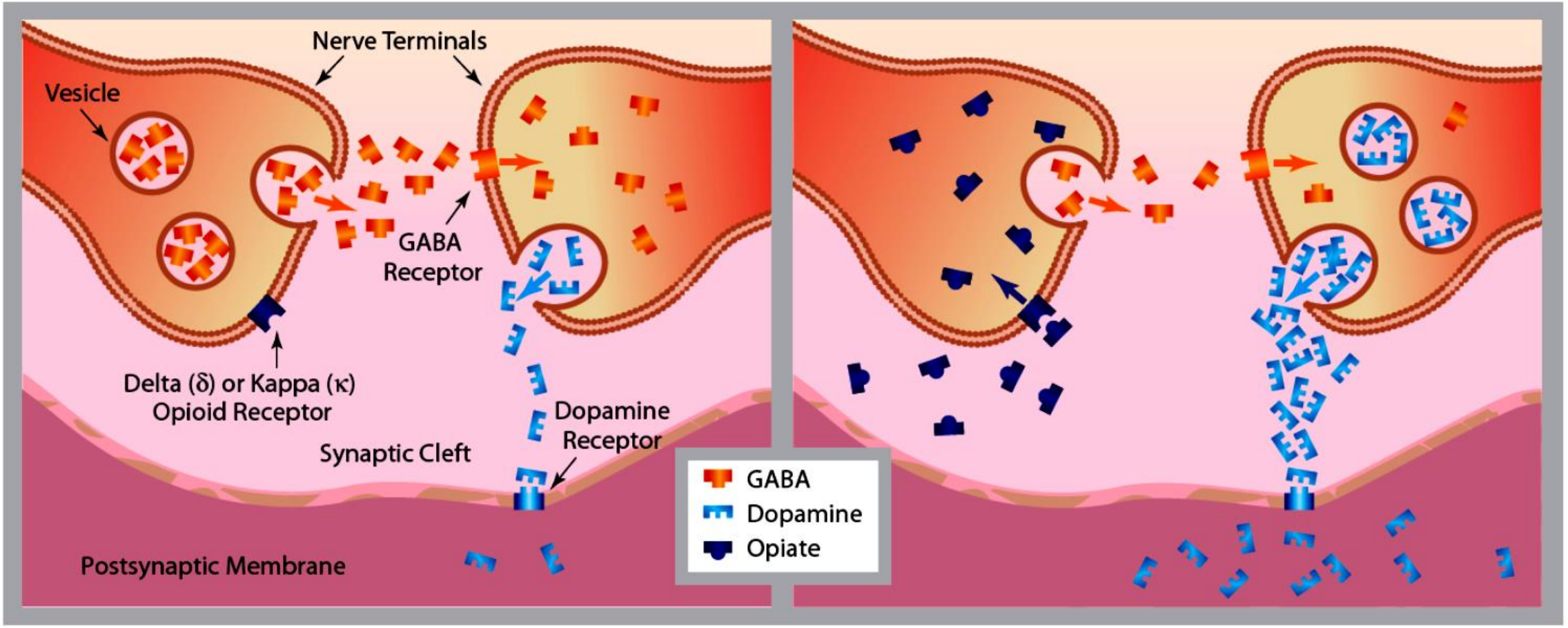


# Mechanism of Toxicity

1

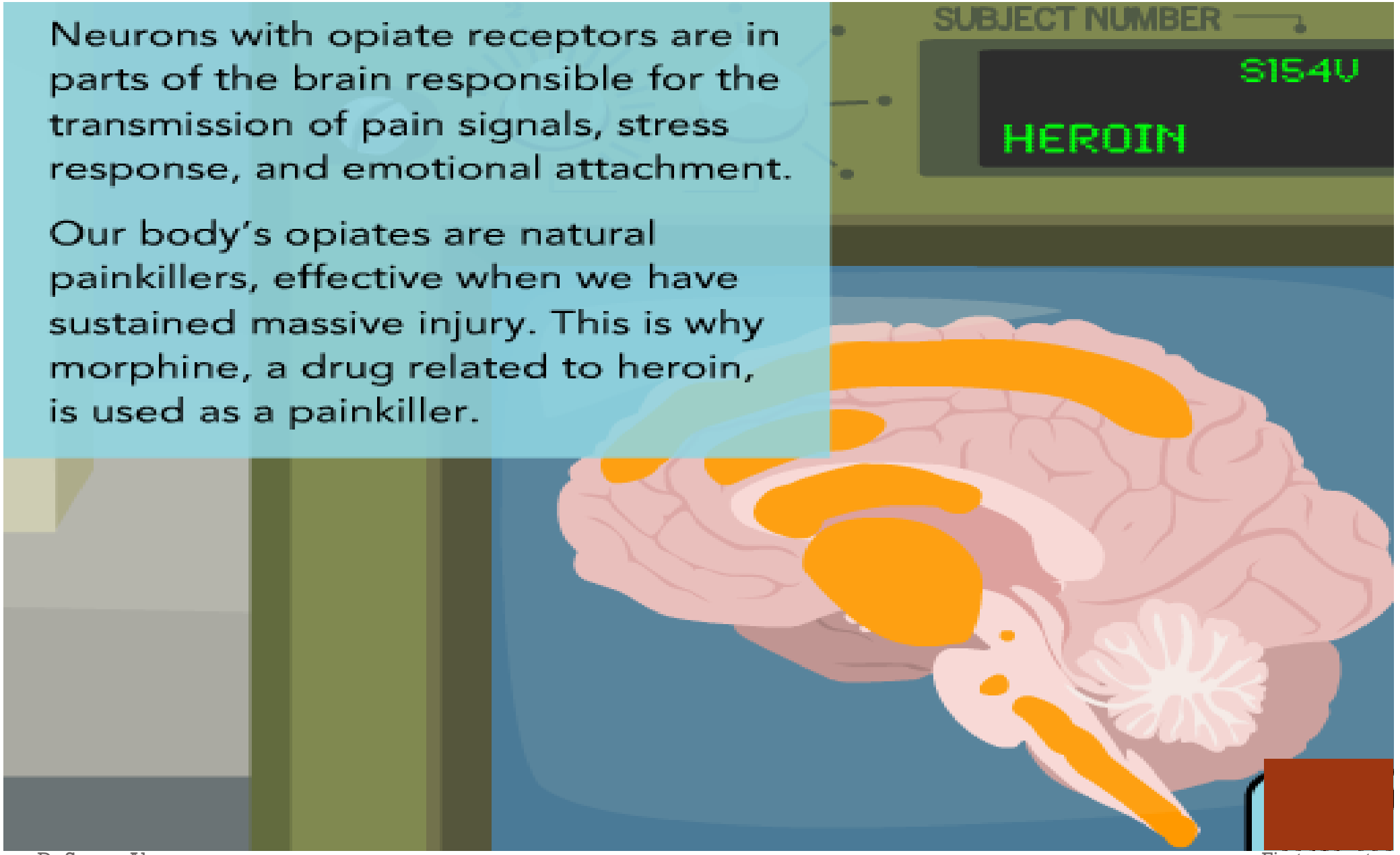



2

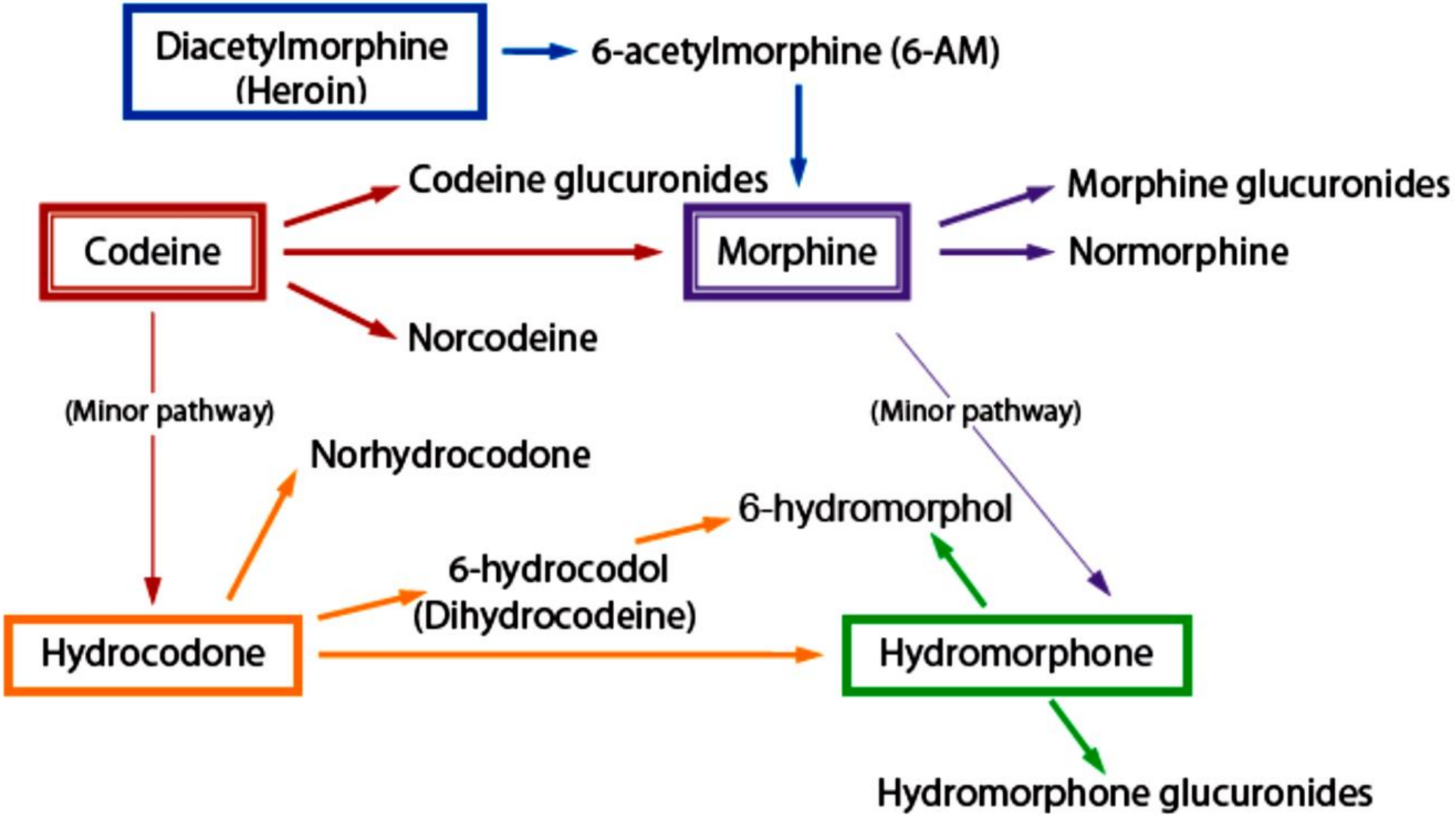

Nerve Terminals
Vesicle
GABA
Receptor
Delta (δ) or Kappa (κ)
Opioid Receptor
Dopamine
Receptor
Synaptic Cleft
Postsynaptic Membrane
GABA
Dopamine
Opiate

Neurons with opiate receptors are in parts of the brain responsible for the transmission of pain signals, stress response, and emotional attachment.

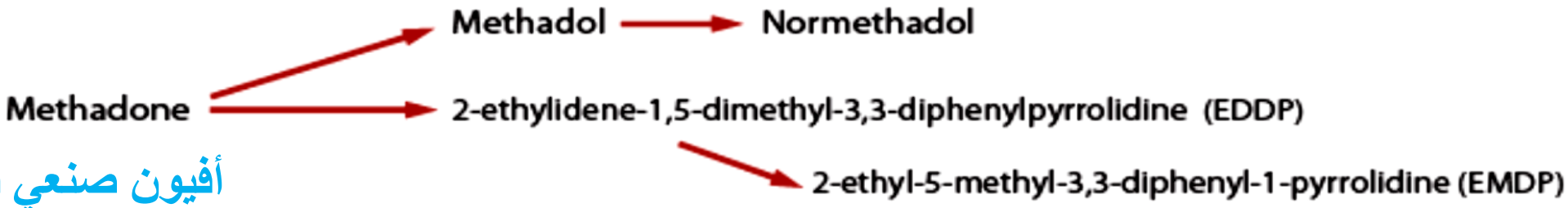
Our body's opiates are natural painkillers, effective when we have sustained massive injury. This is why morphine, a drug related to heroin, is used as a painkiller.



# Opioid Metabolism



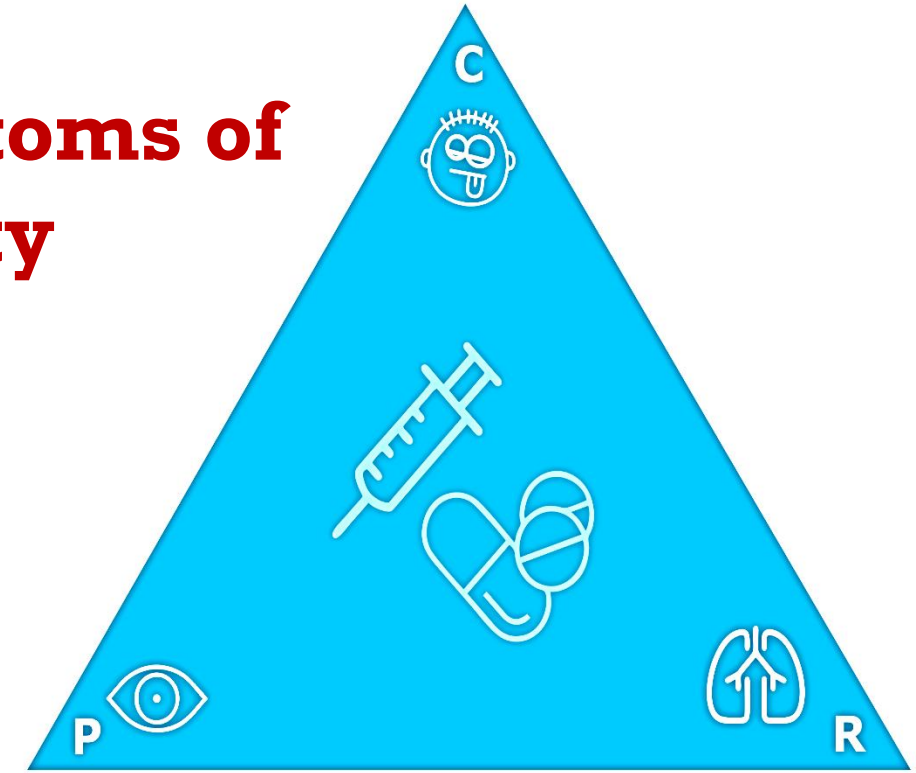
# Opioid Metabolism


أفيون صنعي فموي



## Symptoms of toxicity




## Treatment of toxicity

- **Naloxone**

  Short effect

- **Nalmefene**

  Longer effect

# Heroin

Heroin was first synthesized from morphine in 1874.
Bayer company commercialized heroin as cough suppressant in 1898

Am. J. Ph.] 7 [December, 1901

**BAYER Pharmaceutical Products**

**HEROIN—HYDROCHLORIDE**

is pre-eminently adapted for the manufacture of cough elixirs, cough balsams, cough drops, cough lozenges, and cough medicines of any kind. Price in 1 oz. packages, $4.85 per ounce; less in larger quantities. The efficient dose being very small (1-48 to 1-24 gr.), it is

**The Cheapest Specific for the Relief of Coughs**

(In bronchitis, phthisis, whooping cough, etc., etc.)

WRITE FOR LITERATURE TO

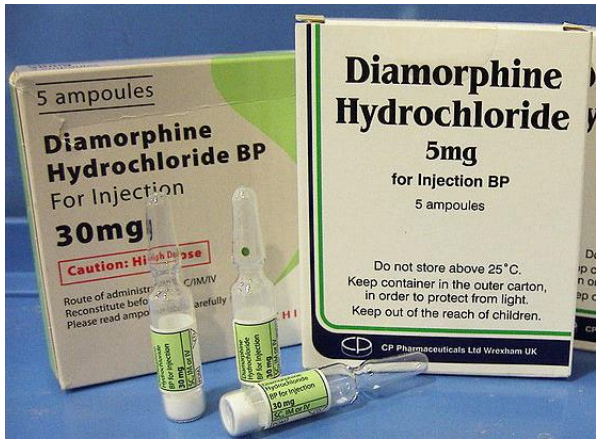
**FARBENFABRIKEN OF ELBERFELD COMPANY**

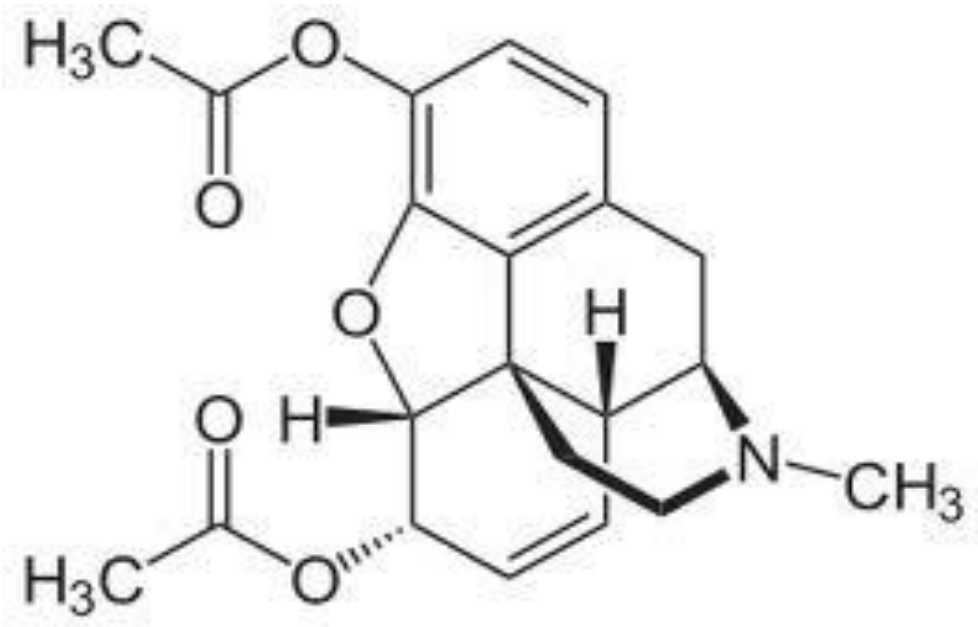
SELLING AGENTS

P. O. Box 2160 40 Stone Street, NEW YORK

# Heroin

**Diamorphine,**
**Diacetylmorphine**




Severe pain management in UK

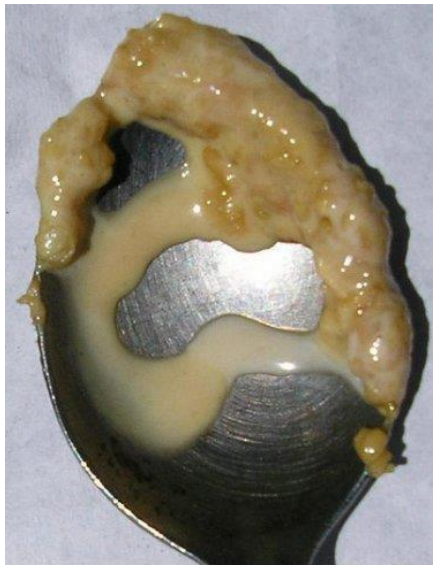
**Semi- Synthetic opioid**

**Opium poppy**

**Cut the seeds**


Milky latex

**Dry**



Gum of raw opium

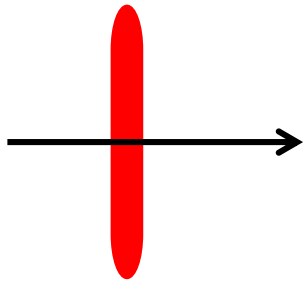
Extraction of morphine

**acetylation**

Heroin

# Heroin

I.V injection , snorting , smoking
Cannot be take orally because of extensive hepatic metabolism



Cross BBB
More powerful than morphine

**Relieve anxiety**

**Break away from reality**

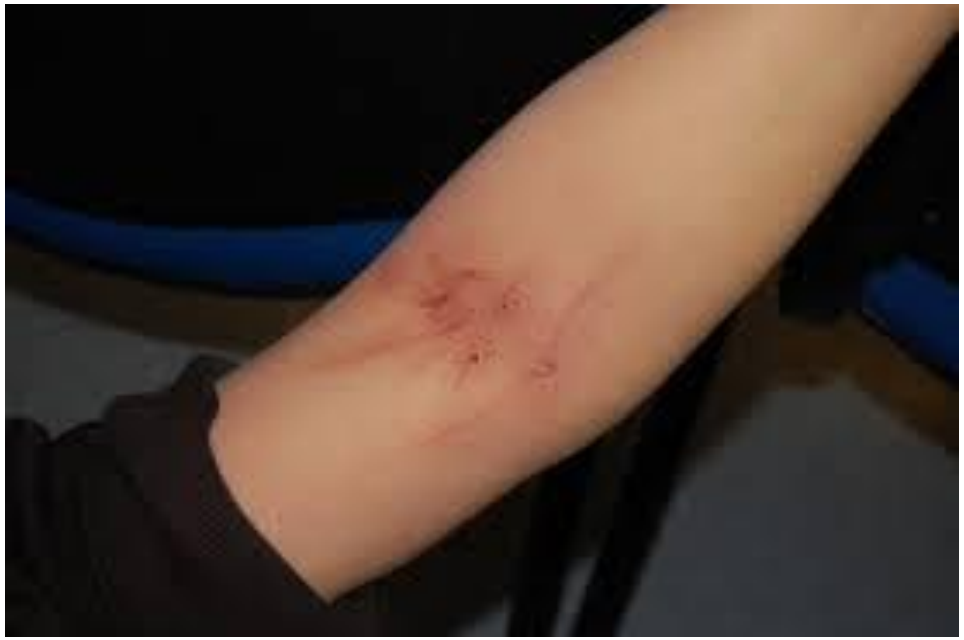
**Euphoria**

**Warm feeling**

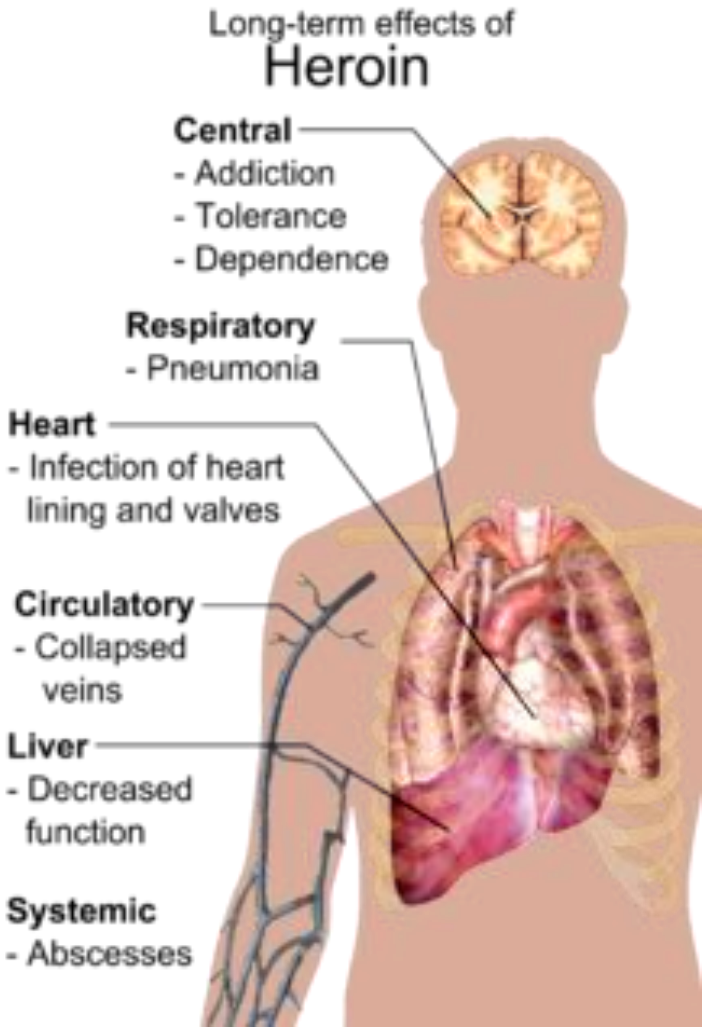
**Addiction**

# Heroin

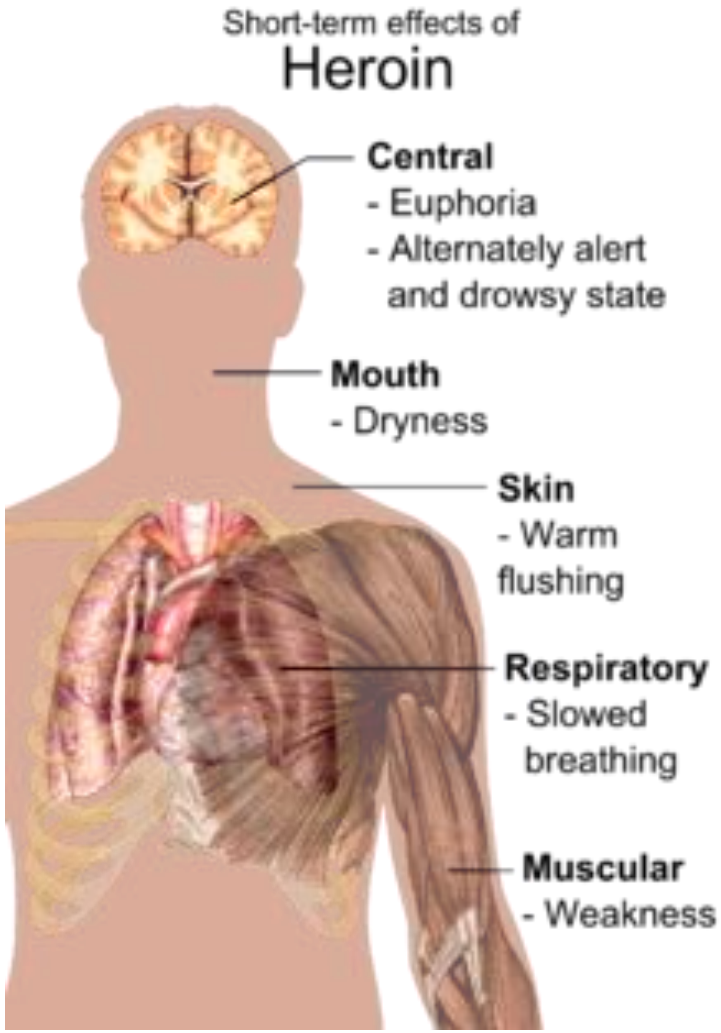
## Signs appear on addicts

# Long term effects

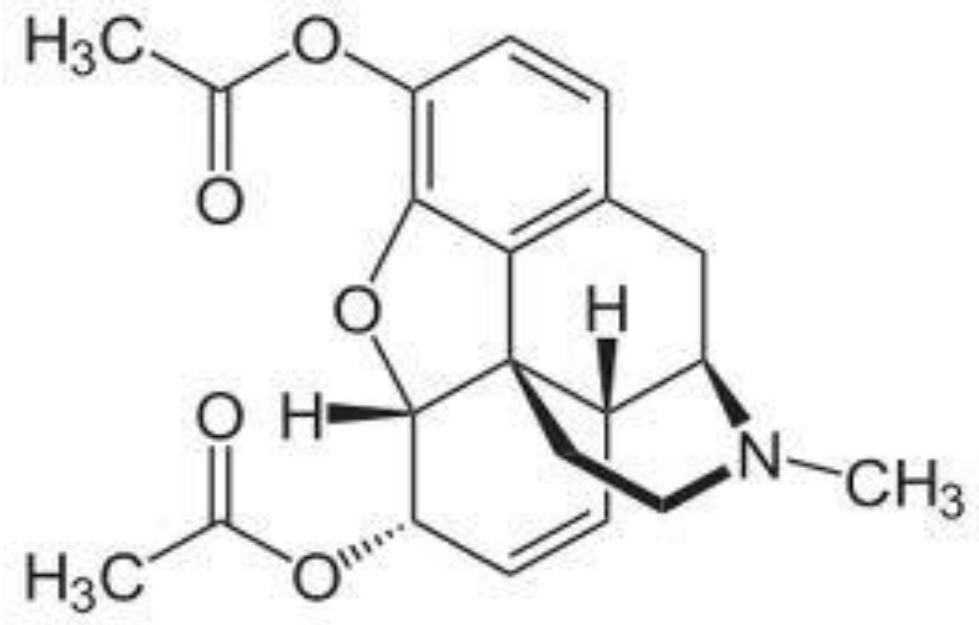



# Short-term effects

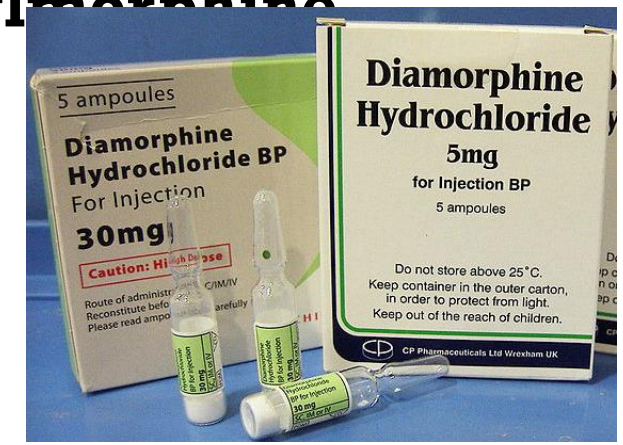


# Heroin

| UK | USA |
|---|---|
| A | Class I |




**Diamorphine,**
**Diacetylmorphine**



# SpeedBall

Heroin

+

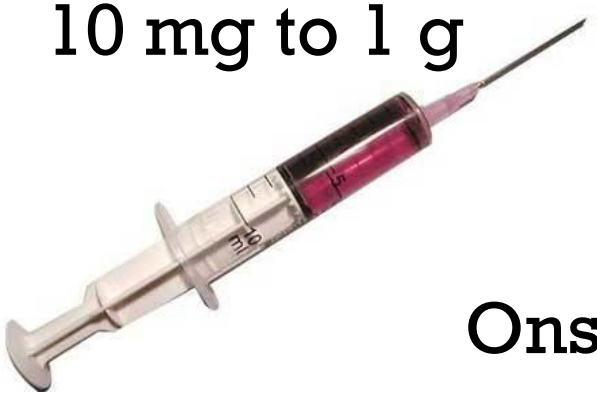
Cocaine

=


Overdoses & death
Severe withdrawal syndrome

# Heroin

10 mg to 1 g



Onset i.v : 1 min

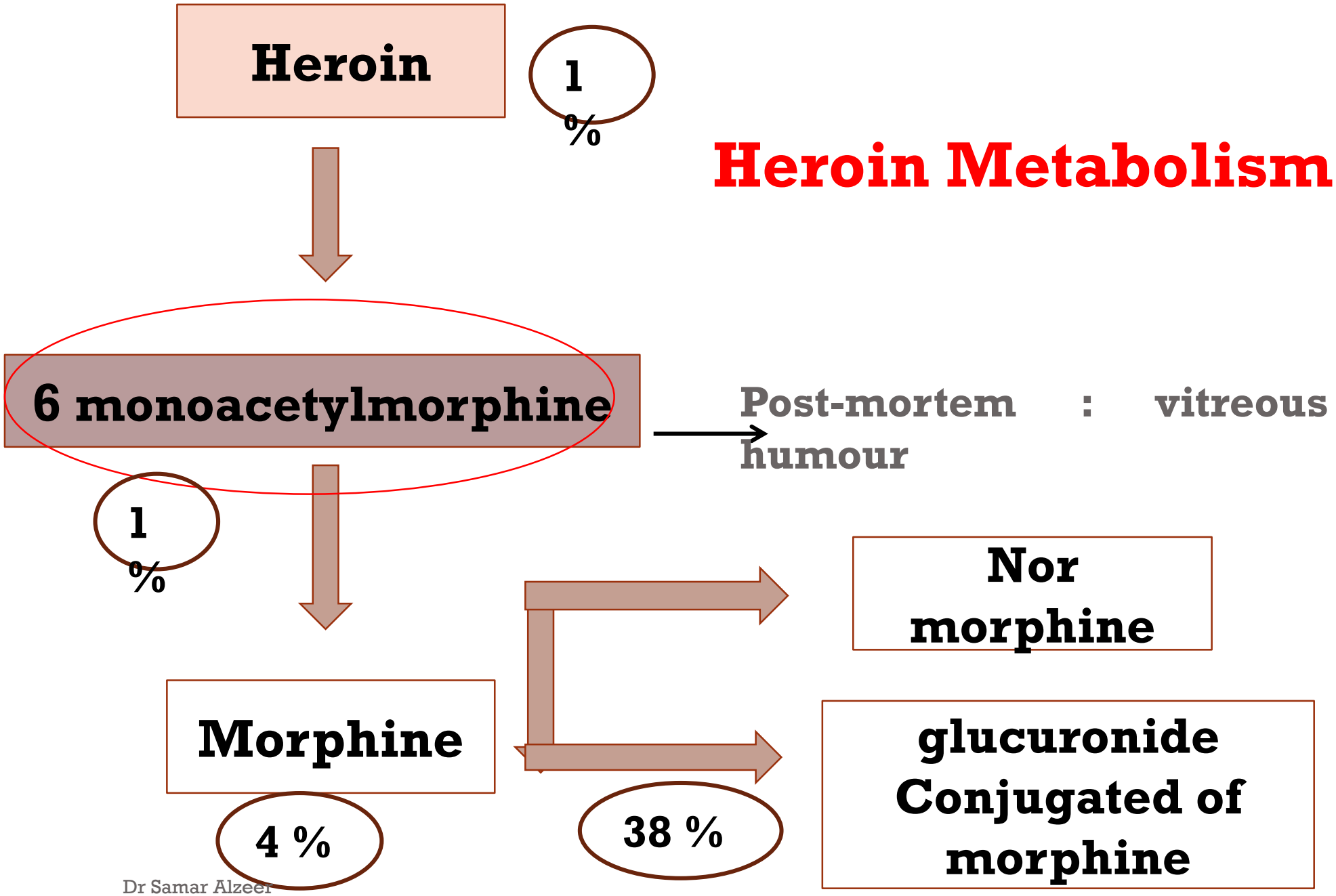
Onset snorting : 5 min

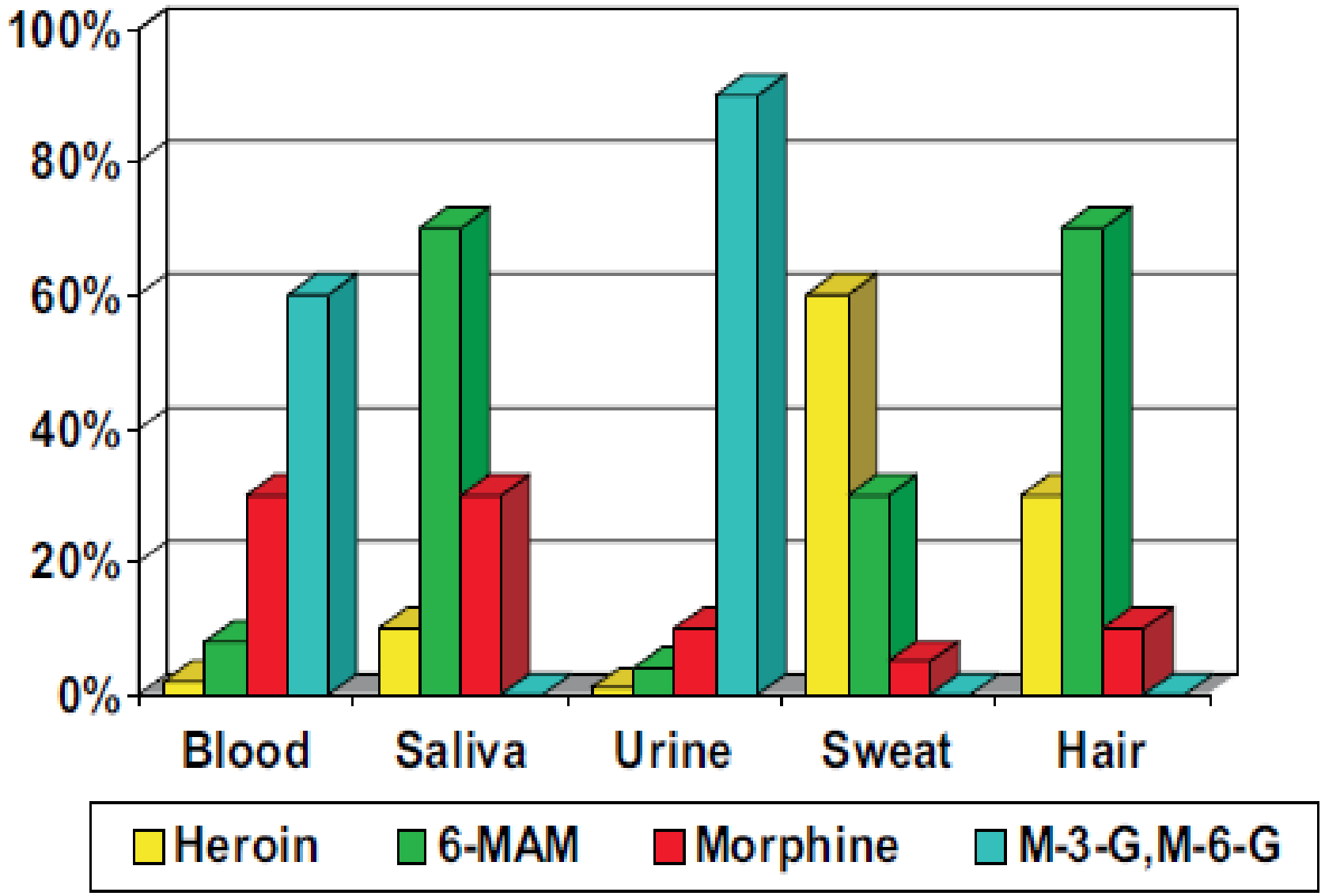
$t\ ½$ = 10 minutes

Metabolism

Elimination in urine

# Heroin Metabolism




100%
80%
60%
40%
20%
0%
Blood
Saliva
Urine
Sweat
Hair
Heroin
6-MAM
Morphine
M-3-G,M-6-G

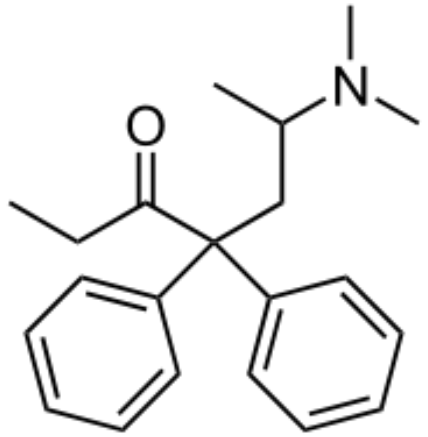
# Detection of Heroin

| Compound | Window of detection in blood | Window of detection in urine | Window of detection in saliva |
|---|---|---|---|
| Morphine | 2-24 hrs | 11-54 hrs | **12-24 hrs** |
| monoacetylmorphine | | 5 hrs | **0.5-8 hrs** |

| | |
|---|---|
| **Colour tests** | Marquis test: Purple red with heroin, morphine & codeine |
| **GC analysis** | Use chloroform as solvent to prevent hydrolysis of heroin |

# Methadone

- Synthetic opioid
- Treatment of heroin addiction
- Oral use




| UK | USA |
|---|---|
| Class A | Schedule II |

# Methadone

**Medical uses**

- Severe pain management (surgery, cancer, burns)
- Cough depressant
- Treatment of addiction

**Desirable Uses**

- Euphoria
- Warm feeling, drowsiness, happiness

**Adverse Effects**

- Tolerance, addiction, withdrawal syndrome
- Hypotension, hypothermia, bradycardia

# Methadone

Large Volume of distribution
Lungs, liver, kidneys, spleen

Protein binding = 87%

T1/2 = 15 hrs

Maxium effect in 4 hrs

**One dose daily 5 mg**

# Elimination of Methadone

**Urine & Bile**

,Methadone, EDDP, EMDP

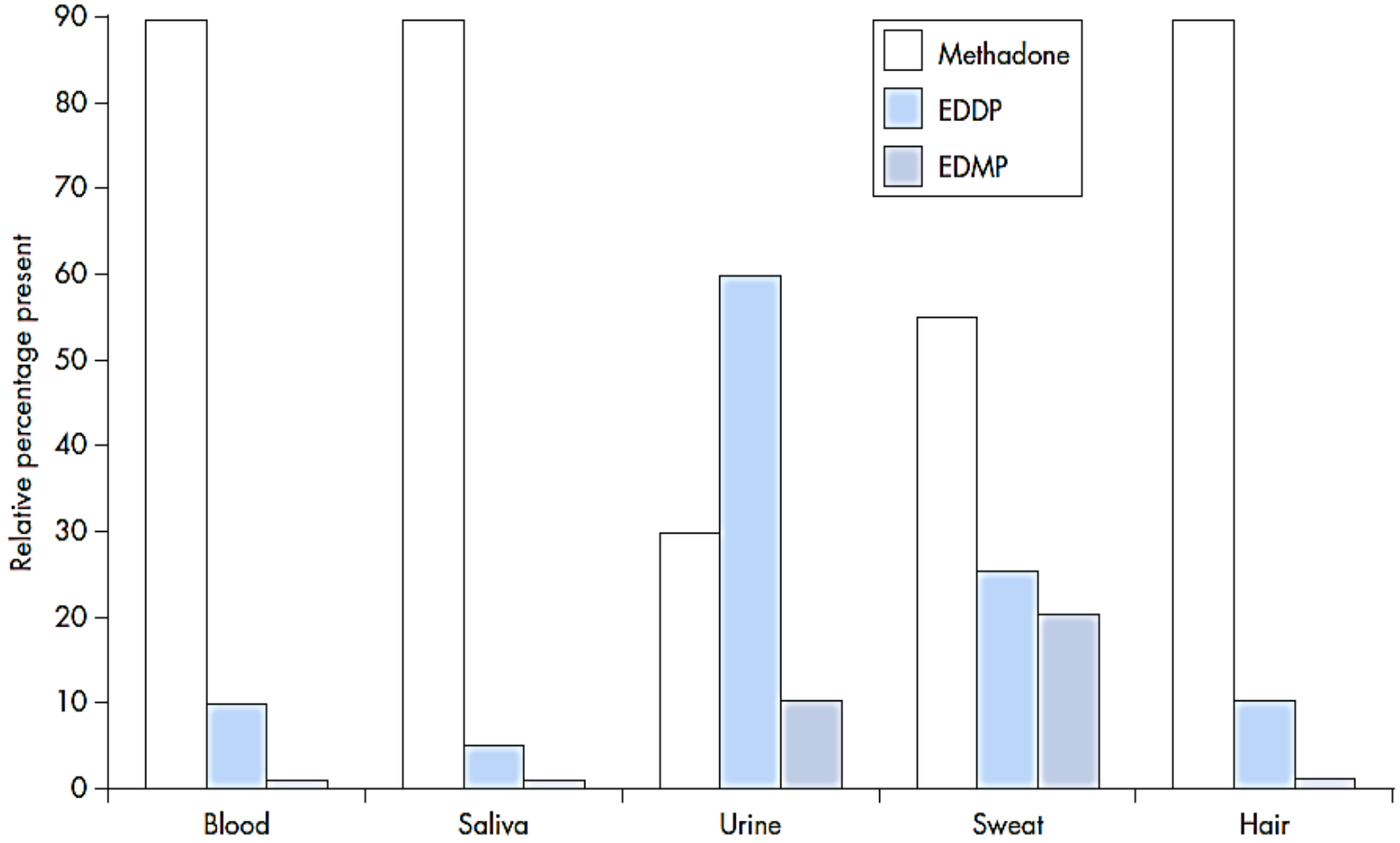
**Urine**

Methadone 5-50%
EDDP : 3-25 %

**pH of urine**

Acidification of urine
Increase elimination from 5 to 22 %

# Methadone


Relative percentage present
90
80
70
60
50
40
30
20
10
0
Methadone
EDDP
EDMP
Blood
Saliva
Urine
Sweat
Hair

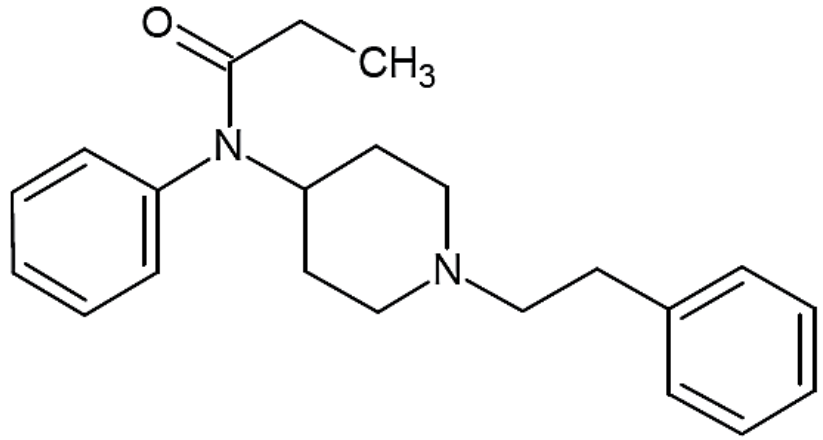
# Methadone

- Marquis test : yellow pink
- Mandolin test
- Cobalt thiocyanate

| Window of detection | Blood | Urine | Saliva |
|---|---|---|---|
| أيام | 24 hours | 3 days | days |

# The Fentanyl Family of Opioids

- Made by Janssen Pharmaceuticals in 1964
- It has several analogues: Alfentanil, Carfentanil, Remifentanil, Sufentanil (Table II)
- Very strong analgesics, used to relieve pain
-
- Quick start and short effect
- Transcutaneous (Patches), Through Mucous Membrane
- Stronger than morphine and heroin. white china



# DRUGS FACILITATED SEXUAL ASSAULT (DFSA)

31

**Dr. Samar Alzeer**

# Drugs Facilitated Sexual Assault (DFSA)

1

- First used in nightclubs
- They are also called Date-Rape drugs

**Why they are used?**

2

- Control the victim and weaken her resistance
- The intensity of DFSA effects are increased in the presence of alcohol

**Characters**

3

- Colourless, odourless, tasteless
- Quick onset
- Victim goes unto coma for a few hours
- DFSA cause hallucinations and amnesia after waking up

# Drugs Facilitated Sexual Assault (DFSA)

**GHB**

**Ketamine**

**Flunitrazepam**

# Gamma hydroxybutyrate (GHB)

**Production**

- It was made in 1960
- Analog to GABA
- Able to cross BBB

**CNS depression**

- Hypnotic
- Analgesic
- Amnesic
- Naturally occurring in the body

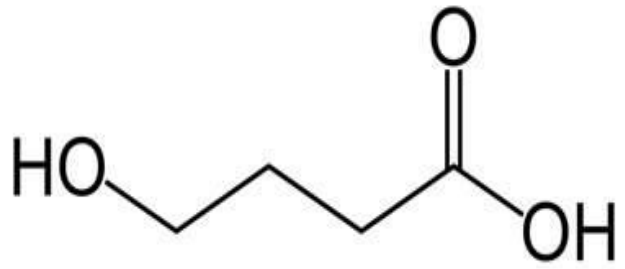
**Usage**

- Oral use ( powder /tablet / solution )
- Odourless /colourless / slightly salty taste that can be covered by any flavoured drinks

# Gamma hydroxybutyrate (GHB)

**Prodrugs**

- gamma butyrolactone (GBL)
- 1.4 butanodiol (1.4 BD)




| التصنيف | أمريكا | بريطانيا |
|---|---|---|
| | Class I | C |

# Gamma hydroxybutyrate (GHB)

**Medical uses**

- Assistant anesthetic
- Given for Narcolepsy under the trade name (Xyrem ®)
- Treat alcoholics (addicted to alcohol) in Italy & Austira under the trade name (Alcover ®)

**GHB Abuse**

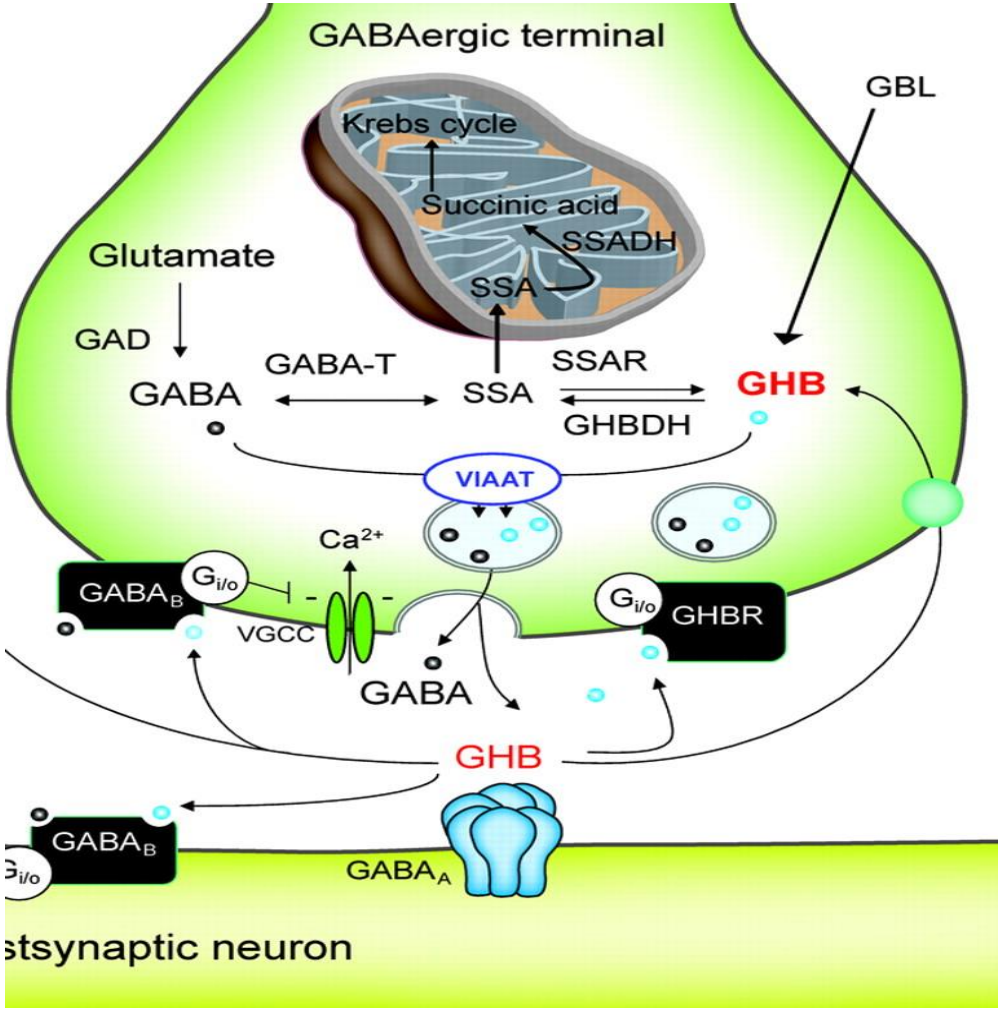
- Anabolic drug (body builders)
- Recreational drug (It is called Liquid Ecstasy)
- Drug facilitated sexual assault (DFSA)

**Adverse effects**

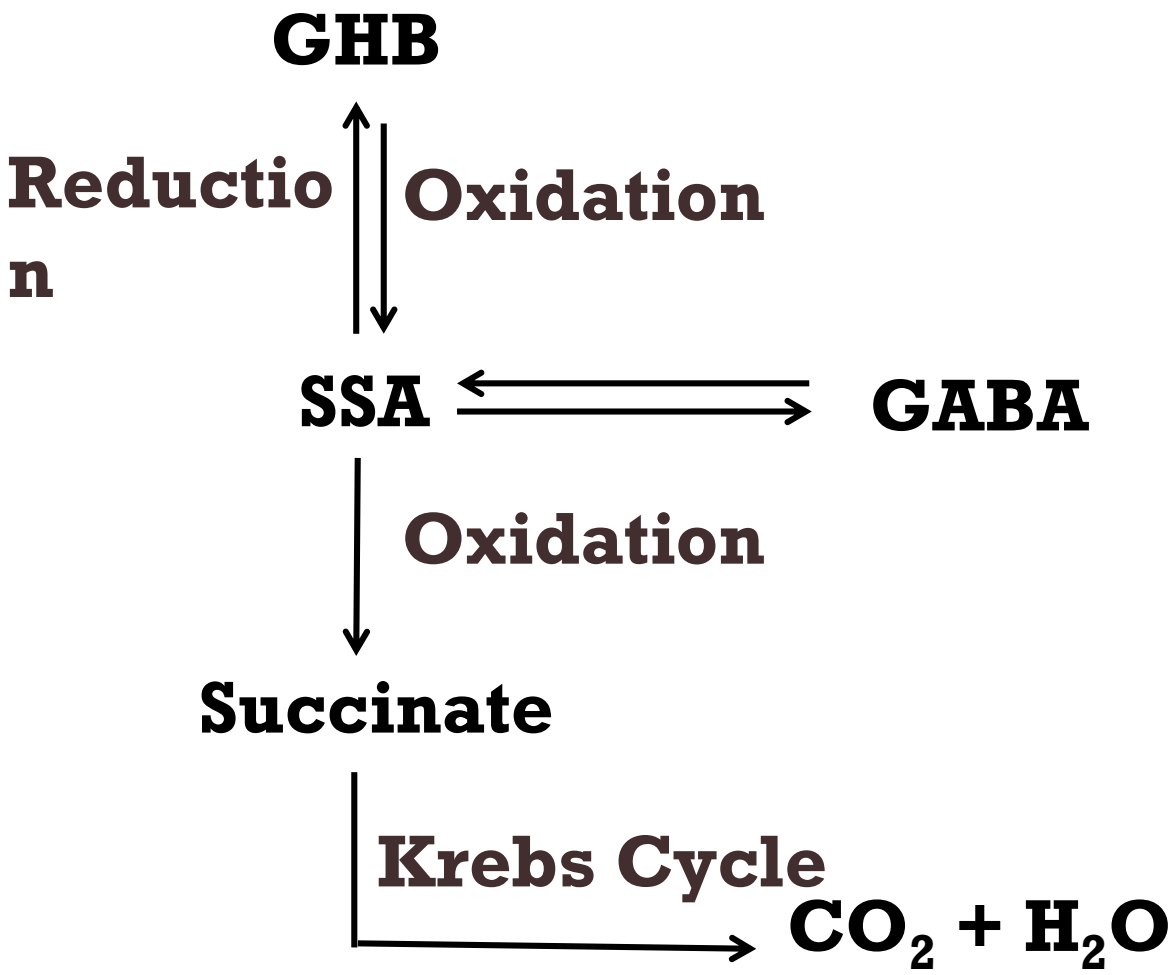
- Amnesia and hallucinations
- Coma
- Respiratory depression

# GHB mechanism of action

- Dose: 1-2 g
- Hypnotic affect of GHB via $GABA_B$ Receptor
- Affect dopamine & serotonin



# GHB toxokinetics




Onset: 15-30 minutes

Half-life ~ 30 minutes

Elimination: less than 5% unchanged in urine

# GHB detection

| Compound | Detection window in blood | Detection window in urine | Detection window in Saliva |
|---|---|---|---|
| GHB | 5 hours | 12-24 hours | 5 hours |

| | |
|---|---|
| **Colour tests** | Gives a purple –pink colour with cobalt nitrate |
| **Enzymatic essay** | Oxidation of GHB to SSA is coupled with reduction of NADP to NADP , and this conversion is monitored at 340 nm |
| **Separation techniques** | GC/MS after derivatization of GHB (to cover polar groups)<br>LC/MS<br>HPLC |

# Flunitrazepam

**Synthesis**

- Roche company (Rohypnol ®)
- Blue colour in water

**CNS depression**

- Benzodiazepines
- Stronger 10 times than diazepam

**Use**

- Oral (syrup / tablets)
- Injection

# Flunitrazepam


| UK | USA |
|---|---|
| C | Class IV |

# Flunitrazepam

**Medical uses**

- Anxiety /Insomnia / depression
- Muscle spasms / convulsions
- analgesic
- Withdrawal syndrome

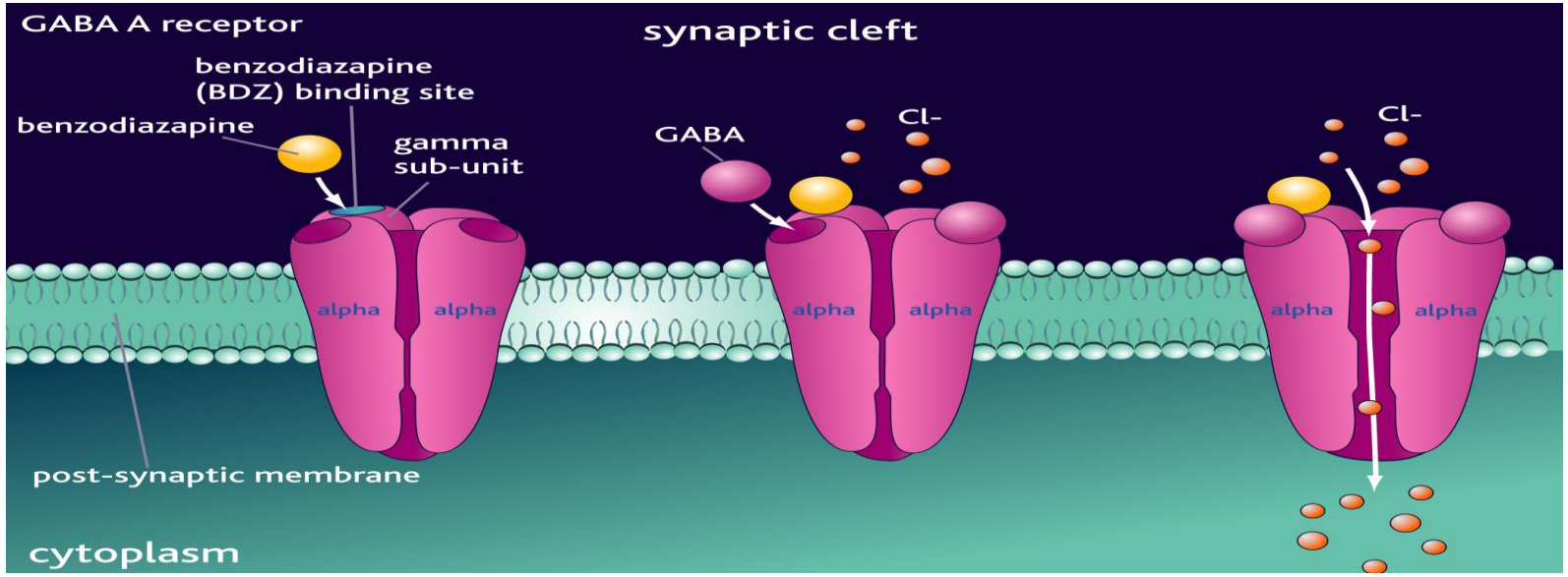
**Desirable effects**

- Ecstasy with heroin or cocaine
- DFSA

**Adverse effects**

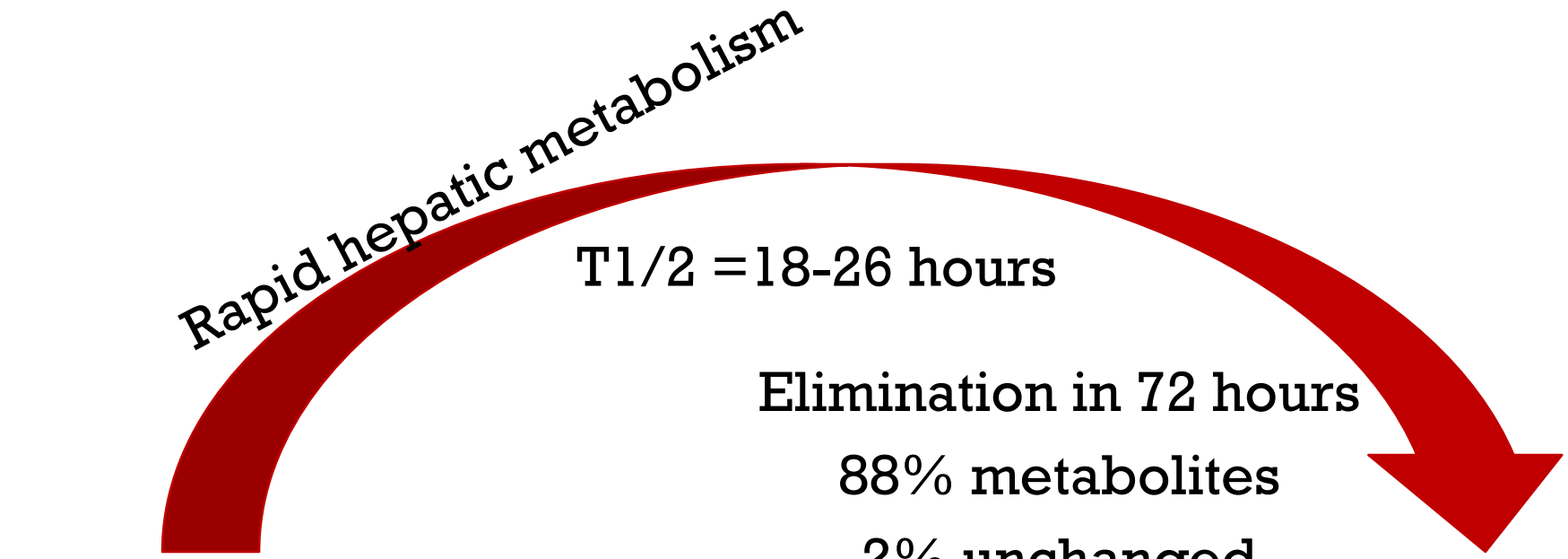
- Vertigo / blurred vision
- Amnesia
- Coma
- Respiratory depression

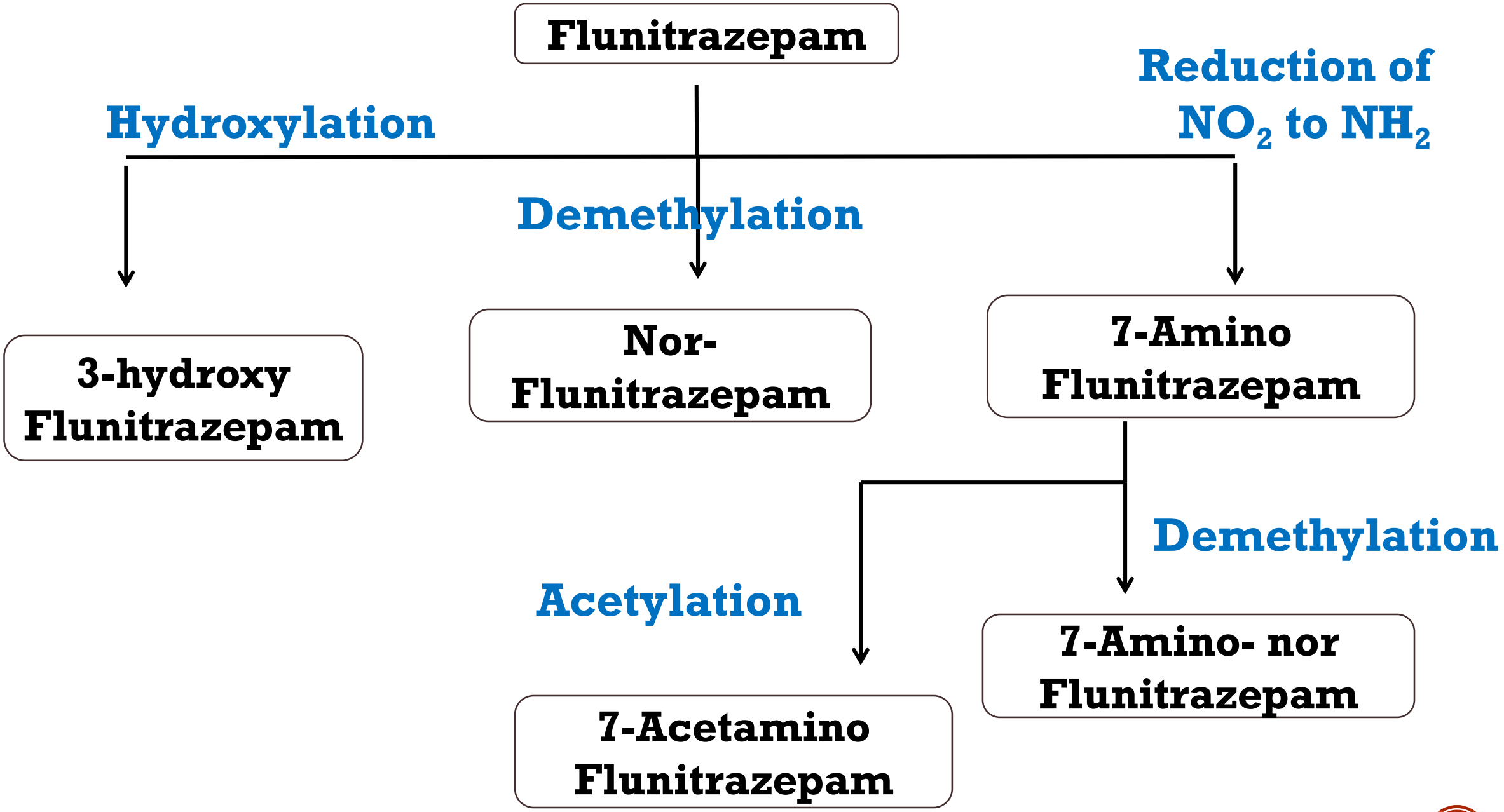
# Mechanism of Toxicity of Flunitrazepam




- $GABA_A$ Receptor ⟶ Cl channels
  - GABA agonist

# Toxicokinetics of Flunitrazepam



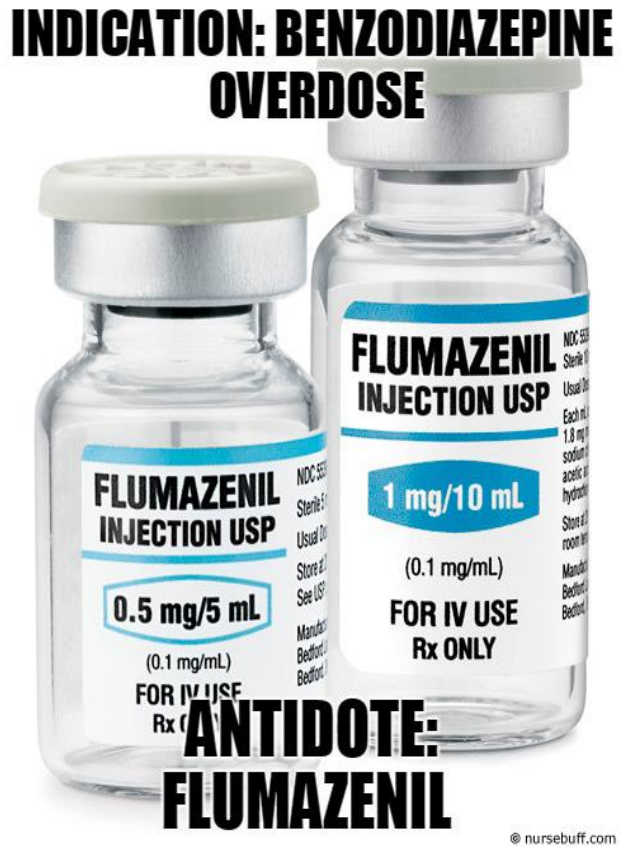

Flunitrazepam
Hydroxylation
Demethylation
Reduction of $NO_2$ to $NH_2$
3-hydroxy Flunitrazepam
Nor-Flunitrazepam
7-Amino Flunitrazepam
Demethylation
Acetylation
7-Amino- nor Flunitrazepam
7-Acetamino Flunitrazepam

# Flunitrazepam Toxicity

- Therapeutic dose diazepam =1-2 mg
- Ataxia, drowsiness, lateral nystagmus, hypotonia, drowsiness, slurred speech and motor incoordination
- paranoia or erratic behaviour, easily aroused, hallucinations, hostility, and seizures
- Severe Toxicity : Unresponsive , coma stage 1 or 2

# Treatment of Benzodiazepines Toxicity

- **Flumazenil (1,4-imidazobenzodiazepine) : antidote**
- Competitive benzodiazepine receptor antagonist
- Flumazenil completely reverses the sedative, anxiolytic, anticonvulsant, ataxic, anesthetic, comatose, and muscle relaxant effects

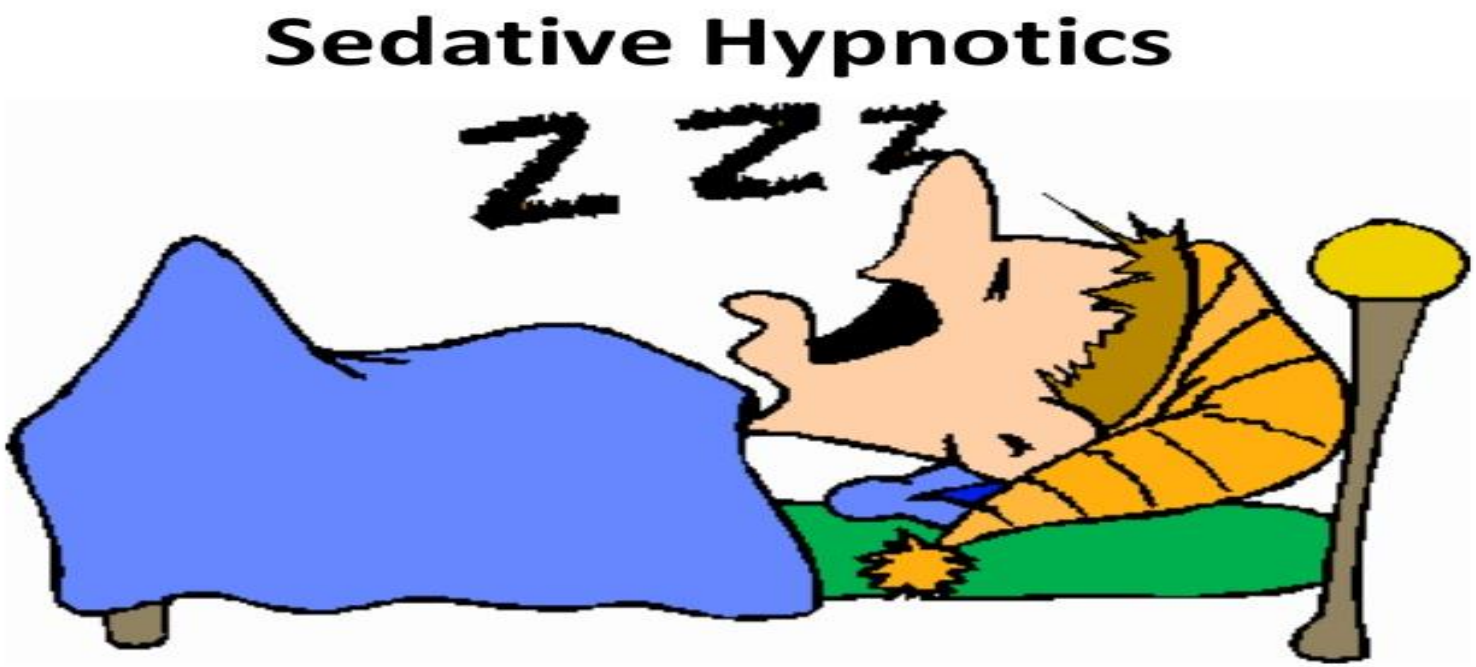


# Flunitrazepam Detection

| | Blood window of detection | Urine window of detection | Saliva window of detection |
|---|---|---|---|
| **Flunitrazepam** | **Few hours** | **72 hours** | 6 hours (low concentration) |
| **7-Amino Flunitrazepam** | 1 day | 14-28 days | 6 hours (low concentration) |

- GC/MS , HPLC ,TLC
- Flunitrazepam + NaOH + DMSO = Pink colour + HCL = Yellow colour
- Flunitrazepam + Denitrobenzene +tetraethyl ammonium hydroxide = oink colour at 590 nm

# Sedative-Hypnotics Toxicity




DR SAMAR ALZEER

# Sedative-Hypnotics

**SEDATIVES**: A drug that calms the person without inducing sleep ( can make the person drowsy).

**HYPNOTICS**: A drug that induces and/or maintains sleep, similar to normal arousal sleep.

**Affect CNS**

- **Barbiturates**
- **Benzodiazepine**
- **Chloral hydrate**
- **Mebrobamate**

# History

- chloral hydrate and meprobamate
- Barbiturates in 1903. Derivatives of barbituric acid

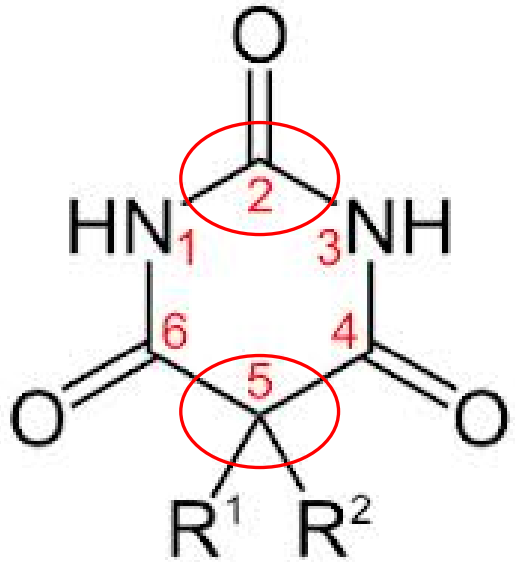
  Barbiturates overdose problems in the 1950s- 1960s
- Benzodiazepines in the 1960s

  Chlordiazepoxide first commercially available benzodiazepine
- Associated with a lot of overdose fatalities
- synergistic effects with ethanol

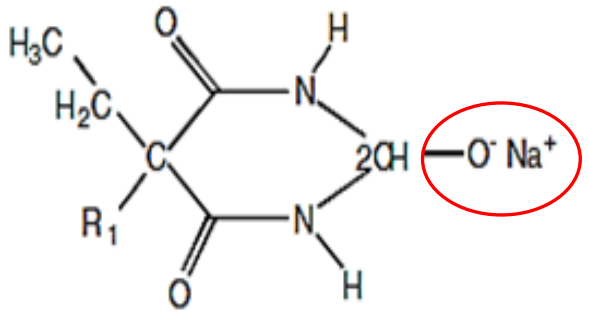
# Barbiturates

- Malonylurea derivatives (diureides)

Malonic acid + urea = barbituric acid




- Weak acids
  - Lipophilic , Pka = 7.2-7.9
- Duration of action




- Dose, mental status , duration of action of the drug, the physical environment , tolerance

# Classification of Barbiturates

## Long acting (LA)

- Mephobarbital
- Phenobarbital

## Short acting (SA)

- Hexobarbital
- Pentobarbital
- Secobarbital

## Intermediate acting (IA)

- Amobarbital
- Aprobarbital
- Butobarbital

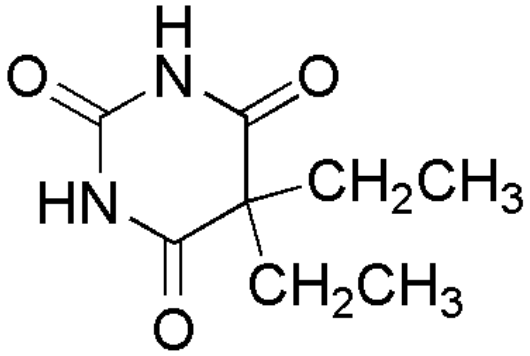
## Ultra- Short acting (UA)

- Thiopental
- Methohexital

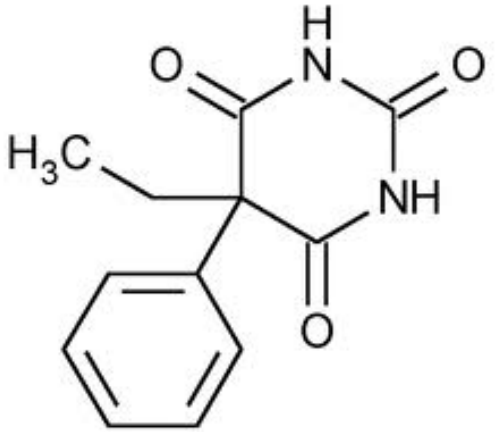
**TABLE II–13. BARBITURATES**

| Drug | Normal Terminal Elimination Half-life (h) | Usual Duration of Effect (h) | Usual Hypnotic Dose, Adult (mg) | Minimum Toxic Level (mg/L) |
|---|---|---|---|---|
| **Ultra–short-acting** | | | | |
| Methohexital | 3–5 | <0.5 | 50–120 | >5 |
| Thiopental | 8–10 | <0.5 | 50–75 | >5 |
| **Short-acting** | | | | |
| Pentobarbital | 15–50 | >3–4 | 50–200 | >10 |
| Secobarbital | 15–40 | >3–4 | 100–200 | >10 |
| **Intermediate-acting** | | | | |
| Amobarbital | 10–40 | >4–6 | 65–200 | >10 |
| Aprobarbital | 14–34 | >4–6 | 40–160 | >10 |
| Butabarbital | 35–50 | >4–6 | 100–200 | >10 |
| Butalbital | 35 | | 100–200 | >7 |
| **Long-acting** | | | | |
| Mephobarbital | 10–70 | >6–12 | 50–100 | >30 |
| Phenobarbital | 80–120 | >6–12 | 100–320 | >30 |

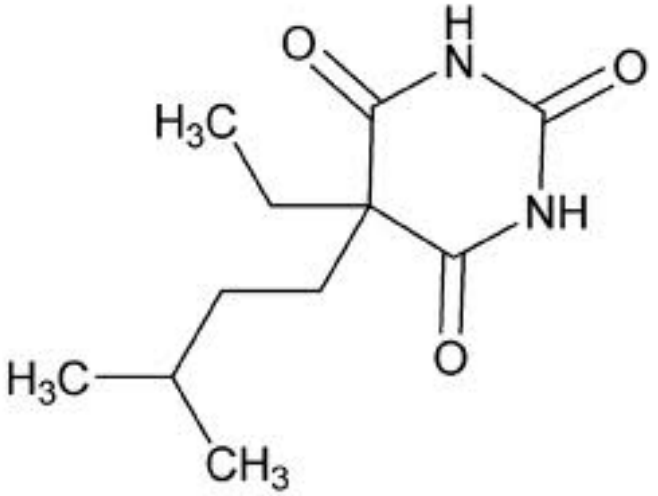
| Drug | R1 | R2 | Notes | Classification (US) |
|---|---|---|---|---|
| Barbital | Ethyl | Ethyl | | Schedule IV |
| Phenobarbital | Phenyl | Ethyl | | Schedule IV |
| Amobarbital | Isopentyl | Ethyl | | Schedule II |
| Pentobarbital | 1 methylbutyl | Ethyl | | Schedule II |
| Secobarbital | 1 methylbutyl | Allyl | | Schedule II |
| Thiopental | 1 methylbutyl | Ethyl | C2=S | Schedule III |



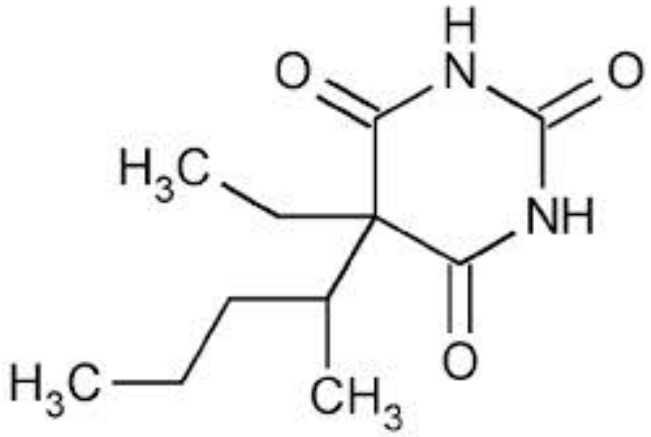
**Barbital**



**Phenobarbital**

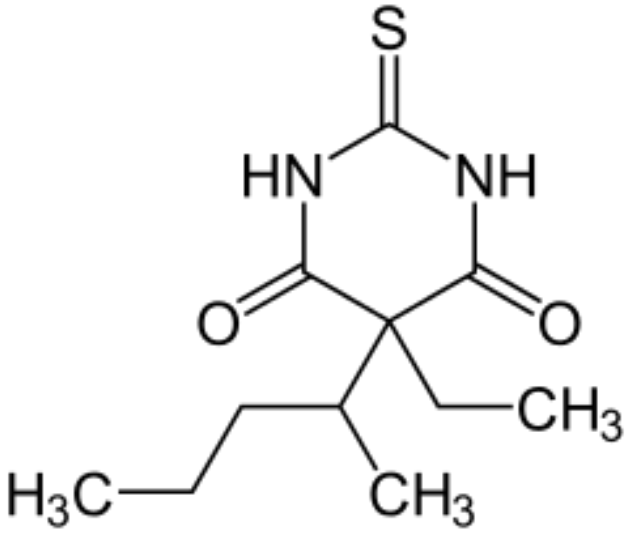


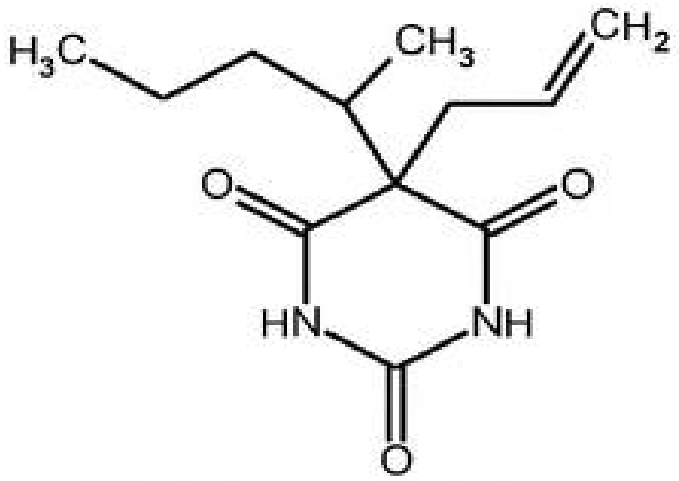
**Amobarbital**



**Pentobarbital**

**Thiopental**





**Secobarbital**

## Short-acting agents

- Highly lipid-soluble
- More protein-binding
- Quick onset
- Shorter effect
- Metabolized in liver in inactive metabolites

## Long-acting agents

- Less lipid-soluble
- Less protein-binding
- Slower onset
- Longer effect
- A percentage of the parent drug is eliminated unchanged in urine

# Barbiturates

- increase in the number of carbons and bulkier side chains

→ enhanced lipid solubility → Increase toxicity

- Thiopental → MB & S → less acidic → more lipid soluble → Ultrashort

- More lipophilic → rapid metabolism → short action

More lipid soluble → rapid in & out from CNS → Rapid start & end of action

→ shorter action

# Pharmacokinetics of Barbiturates: Absorption

- Orally: 100% bioavailability and an onset of action ranging from 10 to 60 min.
- Sodium salts are more rapidly absorbed than free acids.
- Intramuscular injections of sodium salts should be made deep into the muscle to prevent pain and tissue damage.
- Barbiturates utilized for the induction and maintenance of anaesthesia (thiopental) are administered intravenously.

# Pharmacokinetics of Barbiturates: Distribution

- Widely distributed

- Redistribution of US barbiturates (Iv administration) ⟶ Drug goes to muscle and adipose tissues ⟶ Concentrations are decreased in brain and blood ⟶ Patients wake up 5-15 min after thiopental injection

**Pentobarbital**

Protein bound = 65%
VoD = 0.5-1 L/Kg
$T_{1/2}$ = 20-30 hrs

**Amobarbital**

Protein bound = 59%
VoD = 0.9-1.4 L/Kg
T1/2 = 15-40 hrs

**Phenobarbital**

Protein bound = 50 %
VoD = 0.5-0.6 L/Kg
T1/2 = 2-6 days

# Pharmacokinetics of Barbiturates: Metabolism

- The oxidation of substituents at the C-5 position is the most important factor in terminating pharmacological activity

- Oxidation of barbiturates ⟶ formation of alcohols, phenols, ketones, or carboxylic acids ⟶ conjugation with glucuronic acid

- Other metabolic pathways :
  - N-hydroxylation,
  - Desulfuration of thiobarbiturates to oxybarbiturates,
  - Opening of the barbituric acid ring,
  - N-dealkylation of N-alkylbarbiturates to active metabolites, (mephobarbital to phenobarbital)

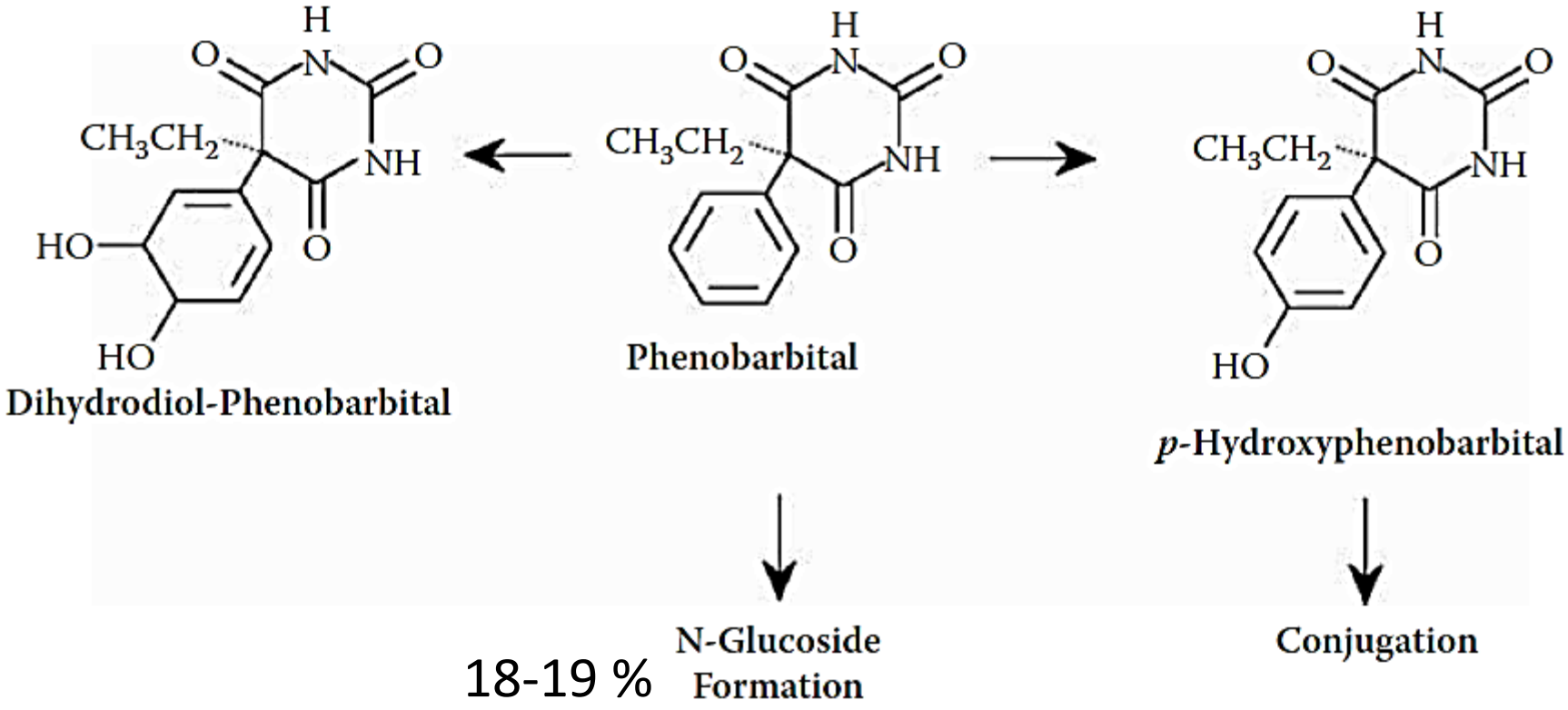
# Pharmacokinetics of Barbiturates:
# Metabolism & Elimination

## Phenobarbital

**Eliminated in urine for 16 days**

25-33% unchanged

18-19 %



# الحرائك الدوائية للباربيتورات

## الاستقلاب والإطراح

**Eliminated in urine for 6 days**

**Pentobarbital**

1 % unchanged in urine

**hydroxylation** → 3´-hydroxypentobarbital and N-hydroxypentobarbital — **85% of dose**

**Oxidation** → Mixtures of alcohols

**No conjugations**

**Amobarbital**

2 % unchanged in urine

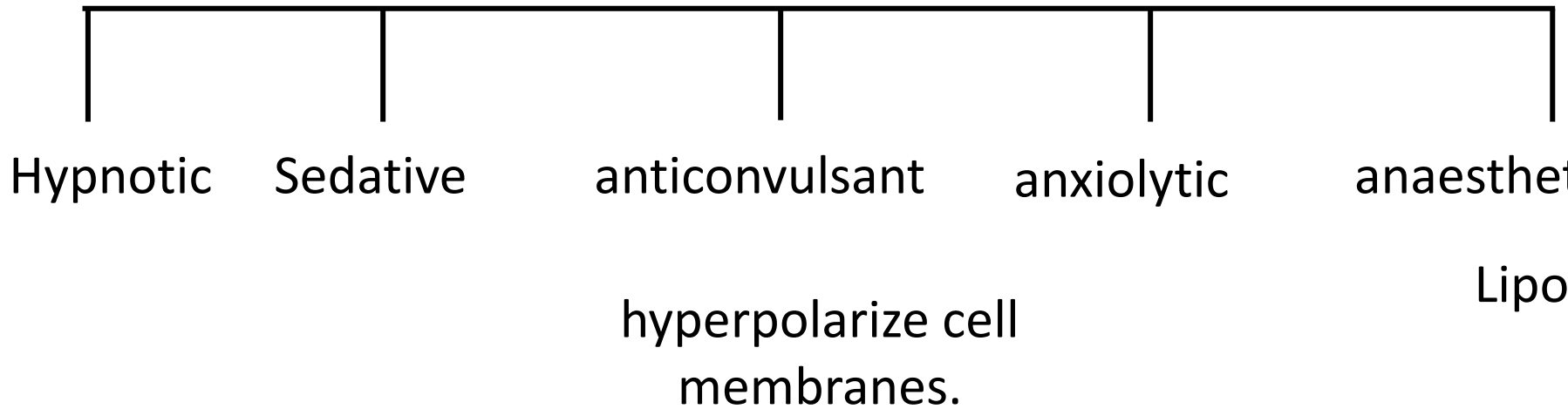
5% unchanged in faeces

**hydroxylation** → 3´-Hydroxyamobarbital — **30-40% in urine**

**Active metabolite**

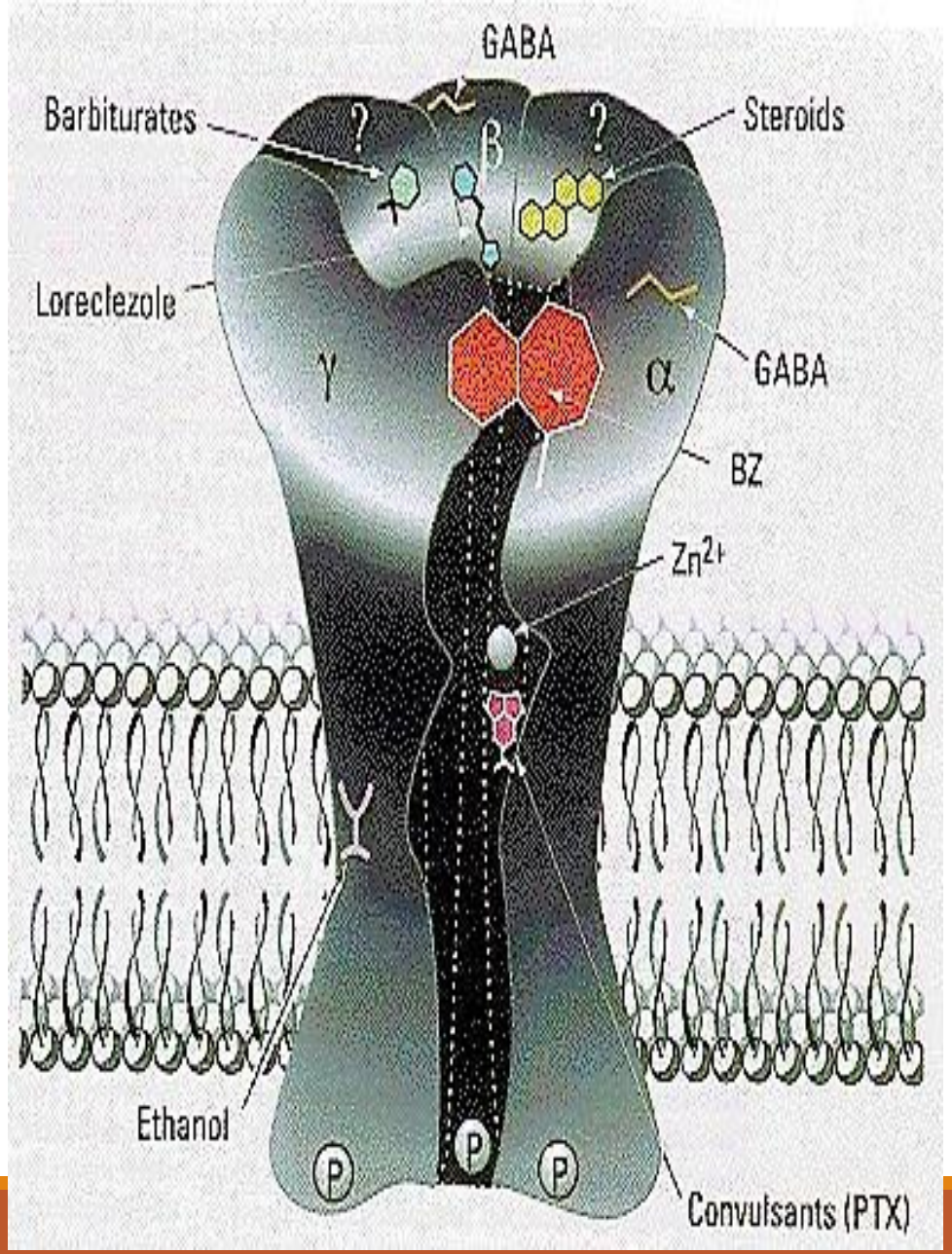
**glycosylation** → *N*-glycosylamobarbital — **29 % in urine**

# Pharmacology of Barbiturates



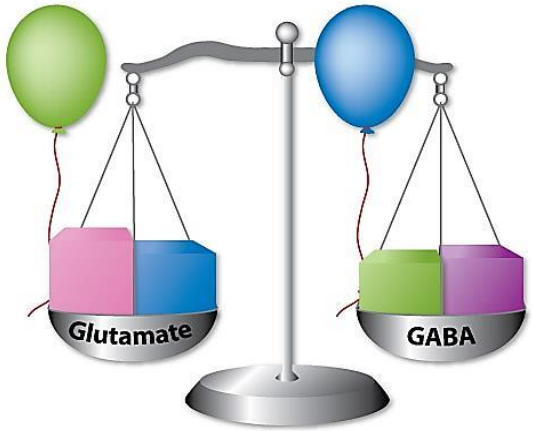

- Induce CYP450

# GABA A receptor



# Pharmacology of Barbiturates

Excitatory synaptic neurotransmission




Inhibitory synaptic neurotransmission

Depress glutamate response.
Glutamate sensitive channel
Calcium channel

Enhance GABA response.
$GABA_A$ Receptor

# آلية سمية الباربيتورات

**GABA receptor**

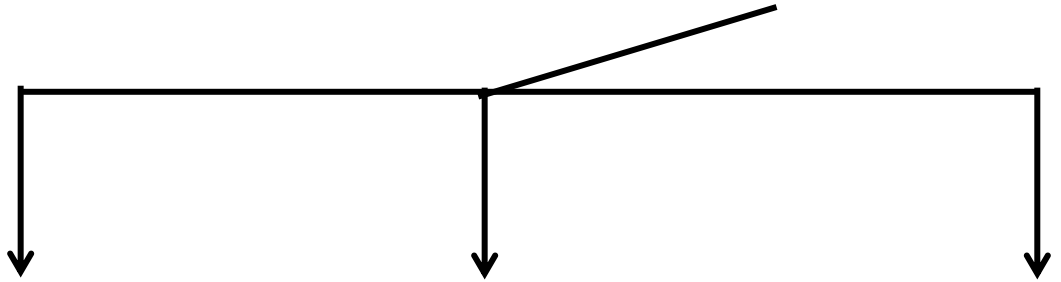
Depress CNS

**Acetylcholine**

smooth, skeletal, cardiac muscle depression

**Respiratory centres**

Depress High dose respiratory centre medullary



neurogenic drive

Chemical drive

Hypoxic drive

# Doses of barbiturates

## Therapeutic doses

- Thiopental dose: 4-20 mg/kg
- Phenobarbital dose: 400 mg daily
- Pentobarbital dose: 100 mg

Toxicity is likely when the dose exceeds 5–10 times the hypnotic dose.

## Toxic doses

- Short-acting : 2-3 g
- Phenobarbital: 6-9 g
- Lethal Injection : 5 g

# Acute Toxicity of barbiturates

- For short & intermediate acting barbiturates
  - Symptoms begin 1-2 hours after ingestion
  - Peak effects are between 4-6 hours.

# Acute Toxicity of barbiturates

**Hypotension**

**Hypothermia**

Hypoxia

Coma

Bradycardia

cardiac depression

Respiratory depression

Coma  blisters: Bullous skin lesions

- Lethargy, slurred speech, nystagmus, and ataxia are common with mild to moderate intoxication. With higher doses, hypotension, coma, and respiratory arrest commonly occur. With deep coma, the pupils are usually small or mid-position; the patient may lose all reflex activity and appear to be dead.

- Complications : pulmonary edema and bronchopneumonia, infiltration with lung abscesses, and renal shutdown.

# Clinical management of acute overdose

- symptomatic
  - Maintaining adequate ventilation
  - keeping the patient warm
  - Supporting vital functions.

- Less than 24 h : gastric lavage, induction of apomorphine emesis, delivery of a saline cathartic or activated charcoal

- Multidose activated charcoal (MDAC) increases the clearance and decreases the half-life of phenobarbital

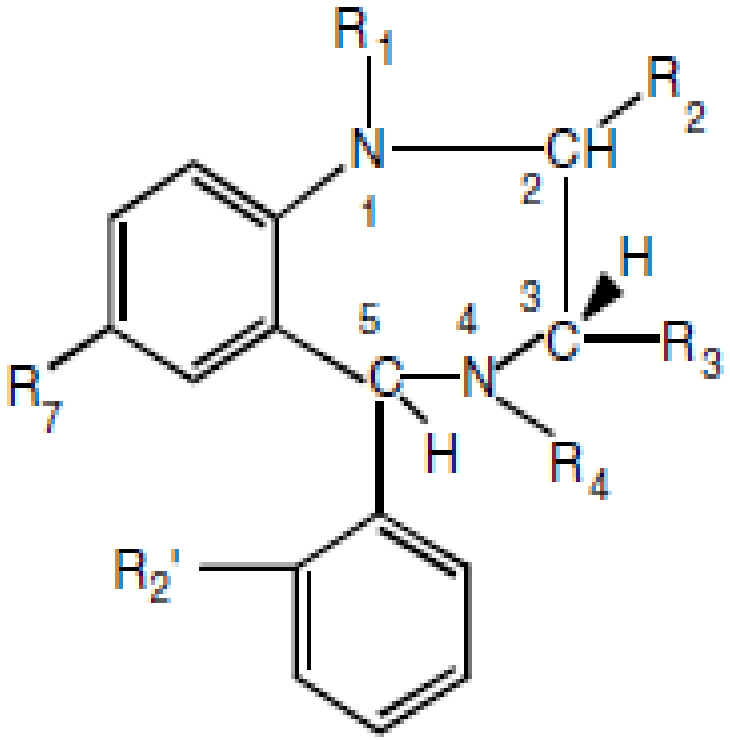
- Alkalinisation of the urine to a pH of 7.5 to 8.0 increases clearance of long-acting barbiturates. Urine alkalinization is contraindicated in patients with renal insufficiency and cerebral or pulmonary edema

- Hemodialysis may be used in life-threatening barbiturate overdose

# Tolerance and withdrawal

- weeks to months
- Decreased effect of barbiturates, even after a single dose
- Sudden withdrawal : development of hallucinations, sleeplessness, vertigo, and convulsions

# Benzodiazepines


- Increased therapeutic index
- Lack of anaesthetic properties
- No Structure-activity relationship
- Active metabolites :R2

| Generic Drug Name | Drug Brand Name(s) |
|---|---|
| alprazolam | Xanax, Xanax XR |
| chlordiazepoxide HCl/clidinium bromide | Librax |
| chlordiazepoxide HCl | Librium |
| chlordiazepoxide HCl/amitriptyline HCl | Limbitrol, Limbitrol DS |
| clobazam | Onfi |
| clonazepam | Klonopin |
| clorazepate | Gen-Xene, Tranxene |
| diazepam | Diastat, Diastat Acudial, Valium, Valtoco |
| estazolam | None |
| flurazepam | None |
| lorazepam | Ativan |
| | Nayzilam, Seizalam |
| oxazepam | None |
| quazepam | Doral |
| temazepam | Restoril |
| triazolam | Halcion |

# Pharmacology of Benzodiazepines

Hypnotic

Sedative

Total sleep time

anticonvulsant

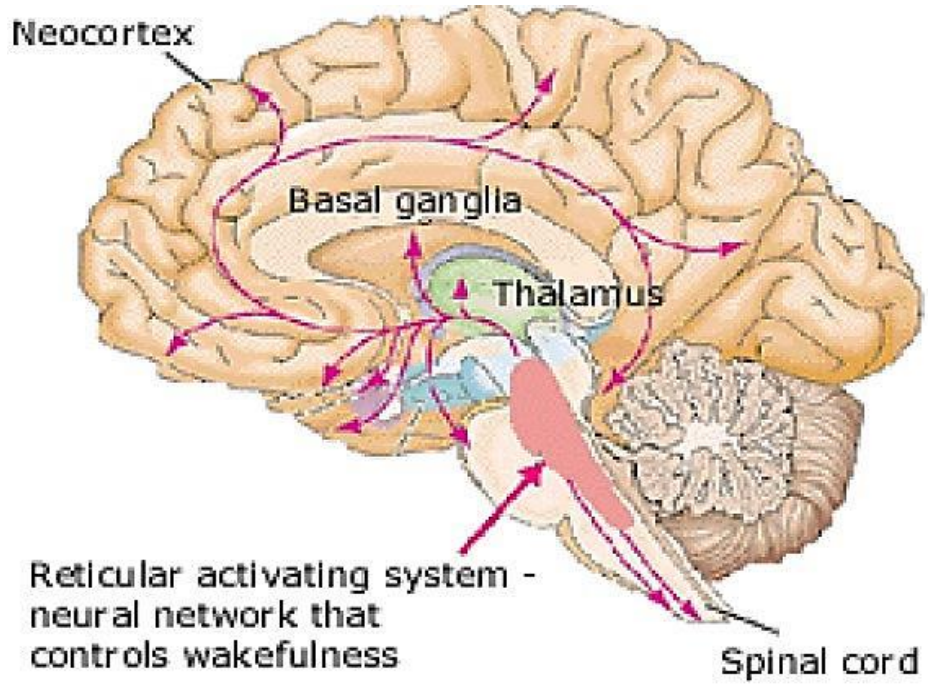
Seizure threshold

anxiolytic

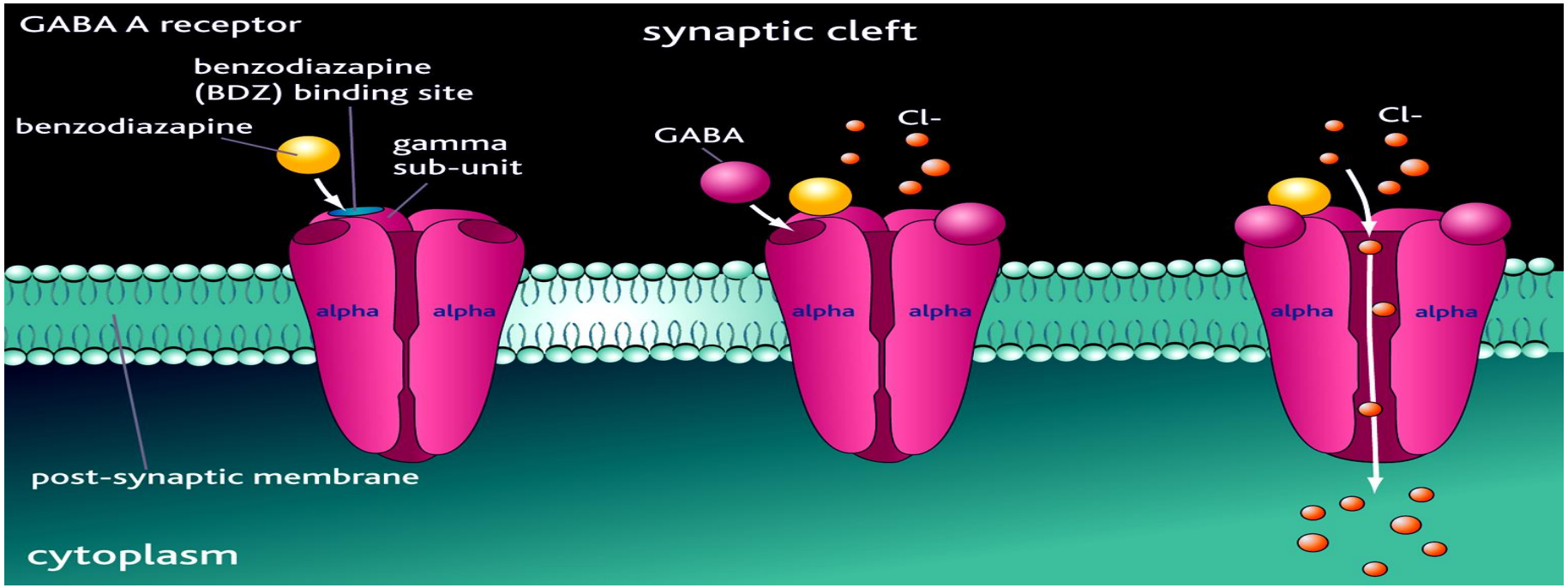
Muscle relaxant

Antidote

- Generalized depression of spinal reflexes and the reticular activating system.
- Clozapine for schizophrenia
- Cross BBB



# Pharmacology of Benzodiazepines

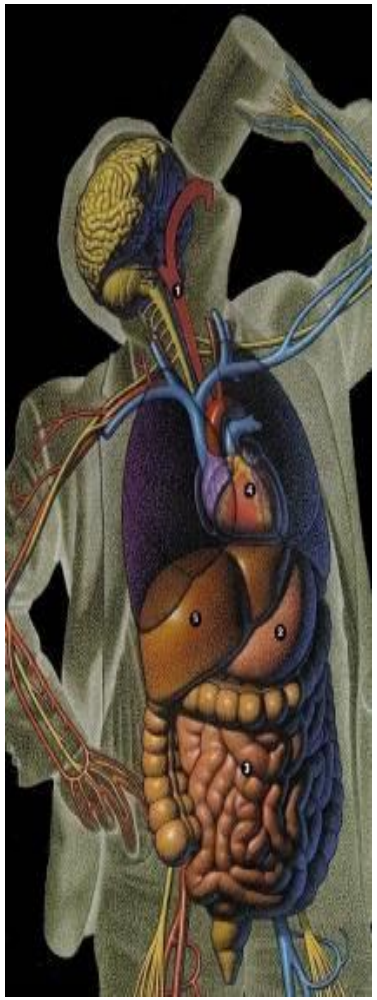



$GABA_A$ receptor ⟶ Cl channels ⟶ Hyperpolarization

## GABA agonist

High doses ⟶ neuromuscular blockade ⟶ vasodilation and hypotension

# Pharmacokinetics of Benzodiazepines



## Diazepam : lipophilic

Oral Bioavailability = 100% → Rapid distribution, Short action

Tmax = 1 h adult/ 15-30 min child

- Lorazepam less lipophilic : Tmax = 2 hours
- Prazepam and clorazepate : prodrugs to nordiazepam
- Benzodiazepine Protein bound = 85-95 %
- VD = 1-3 L/Kg

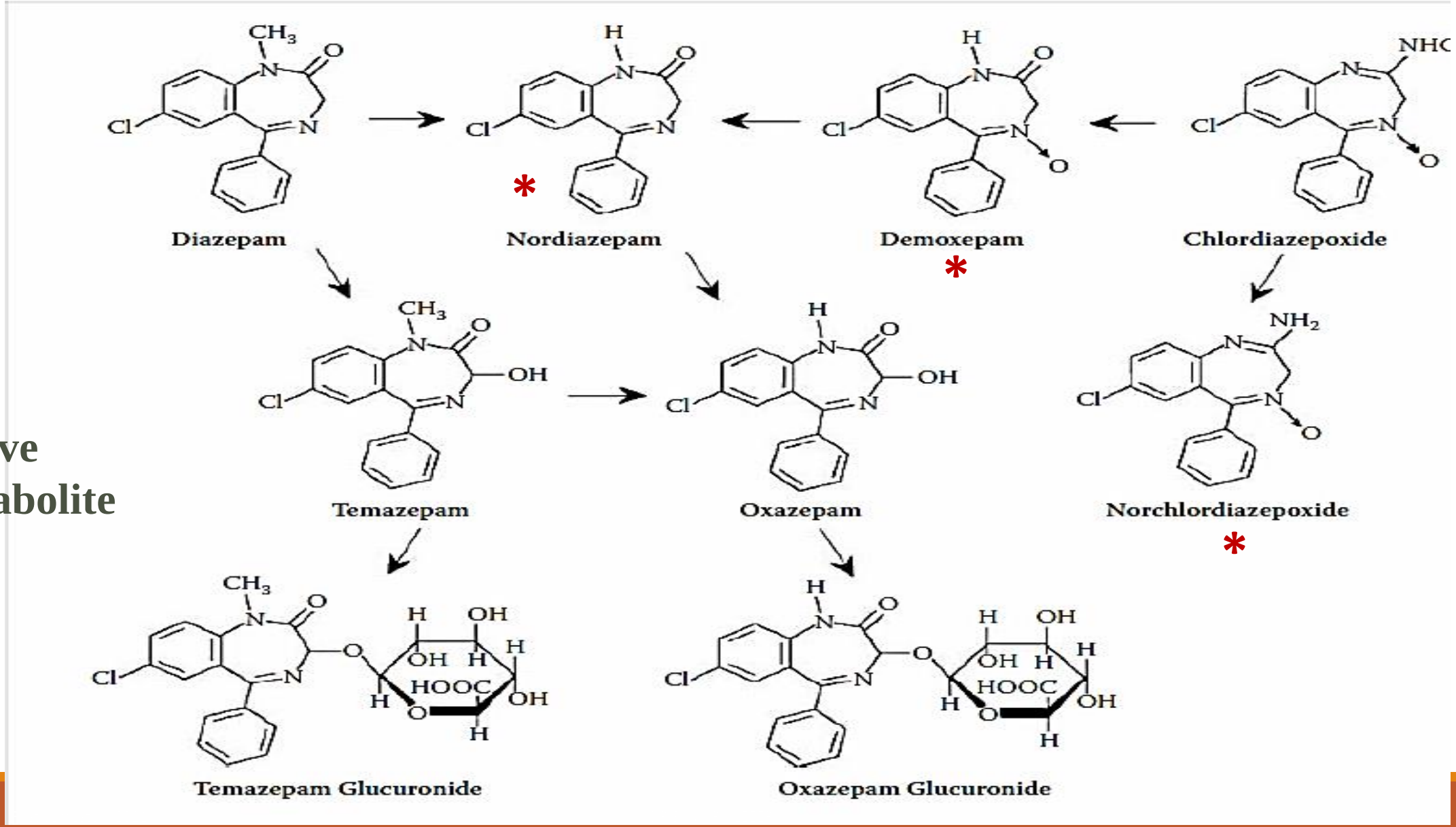
# Pharmacokinetics of Benzodiazepines: Absorption

- Lipophilic acids (diazepam pKa = 3.4)
- Diazepam: highly lipophilic:  is absorbed rapidly,
  Tmax= 1 h in adults and 15 to 30 min in children.
- Diazepam bioavailability : 100 % oral , 50 to 60% intramuscularly or suppositories
- Lorazepam, less lipophilic : slower rates of absorption. Tmax = 2 hours
- Prazepam and clorazepate  are prodrugs to nordiazepam. Slow absorption

# Pharmacokinetics of Benzodiazepines: Distribution

- Two-compartment pharmacokinetic model
- Highly bound to plasma proteins (85 to 95%)
- Lipophilic benzodiazepines distribute more rapidly → Redistribution from CNS
  → Shorter duration of action
- Active metabolites increase duration of action
- No relationship between T1/2 and duration of effect
- CYP450 inhibitors (ketoconazole, nefazodone) increase benzodiazepines blood concentrations

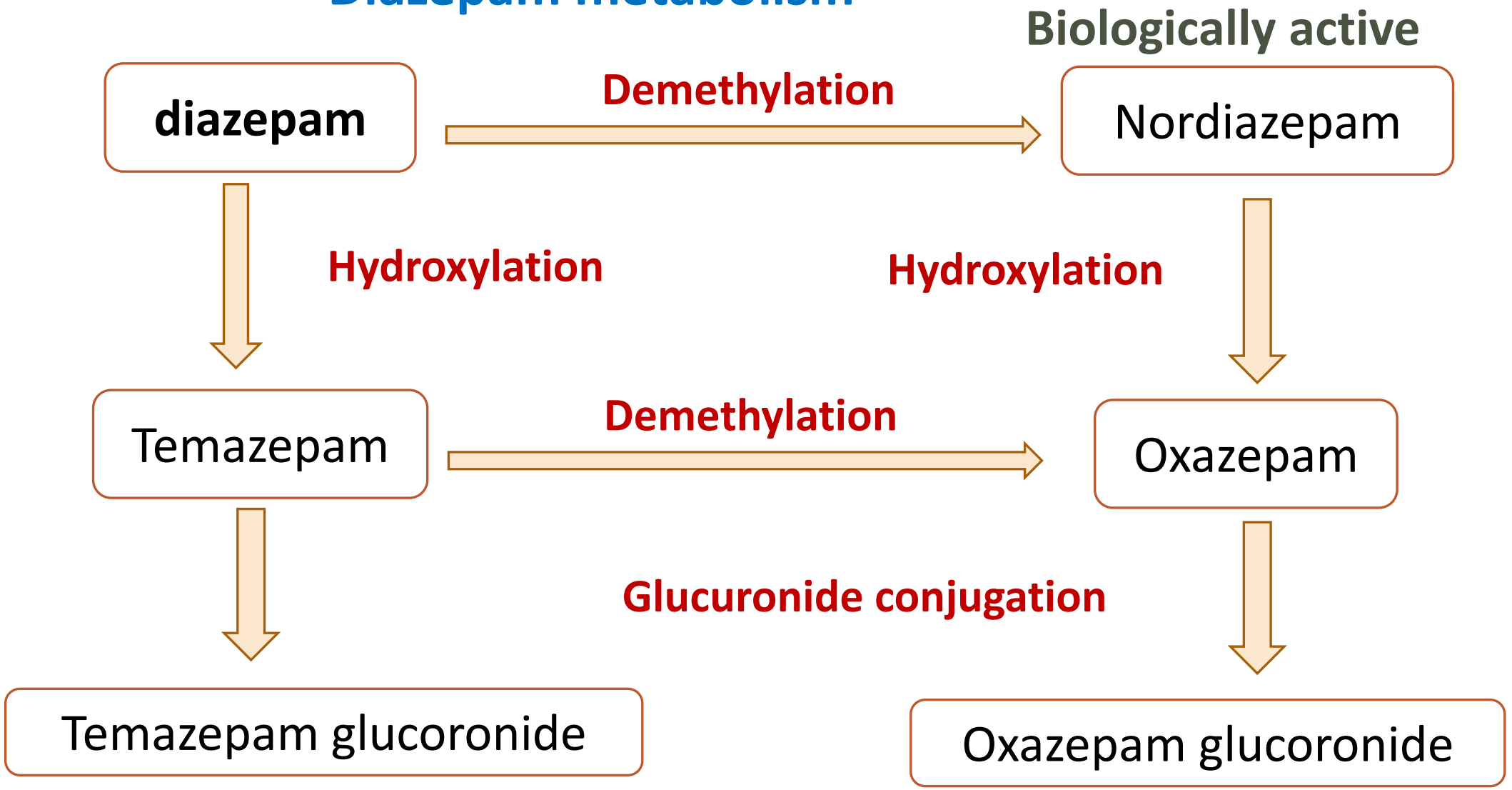
# Metabolism of Benzodiazepines




**Active metabolite**

*

# Diazepam metabolism



# Toxicity of Benzodiazepines

- Therapeutic dose diazepam =2-10 mg
- Toxic dose =15-20 times therapeutic dose
- Ataxia, drowsiness, lateral nystagmus, hypotonia, drowsiness, slurred speech and motor incoordination
- paranoia or erratic behaviour, easily aroused, hallucinations, hostility, and seizures
- Severe Toxicity : Unresponsive , coma stage 1 or 2

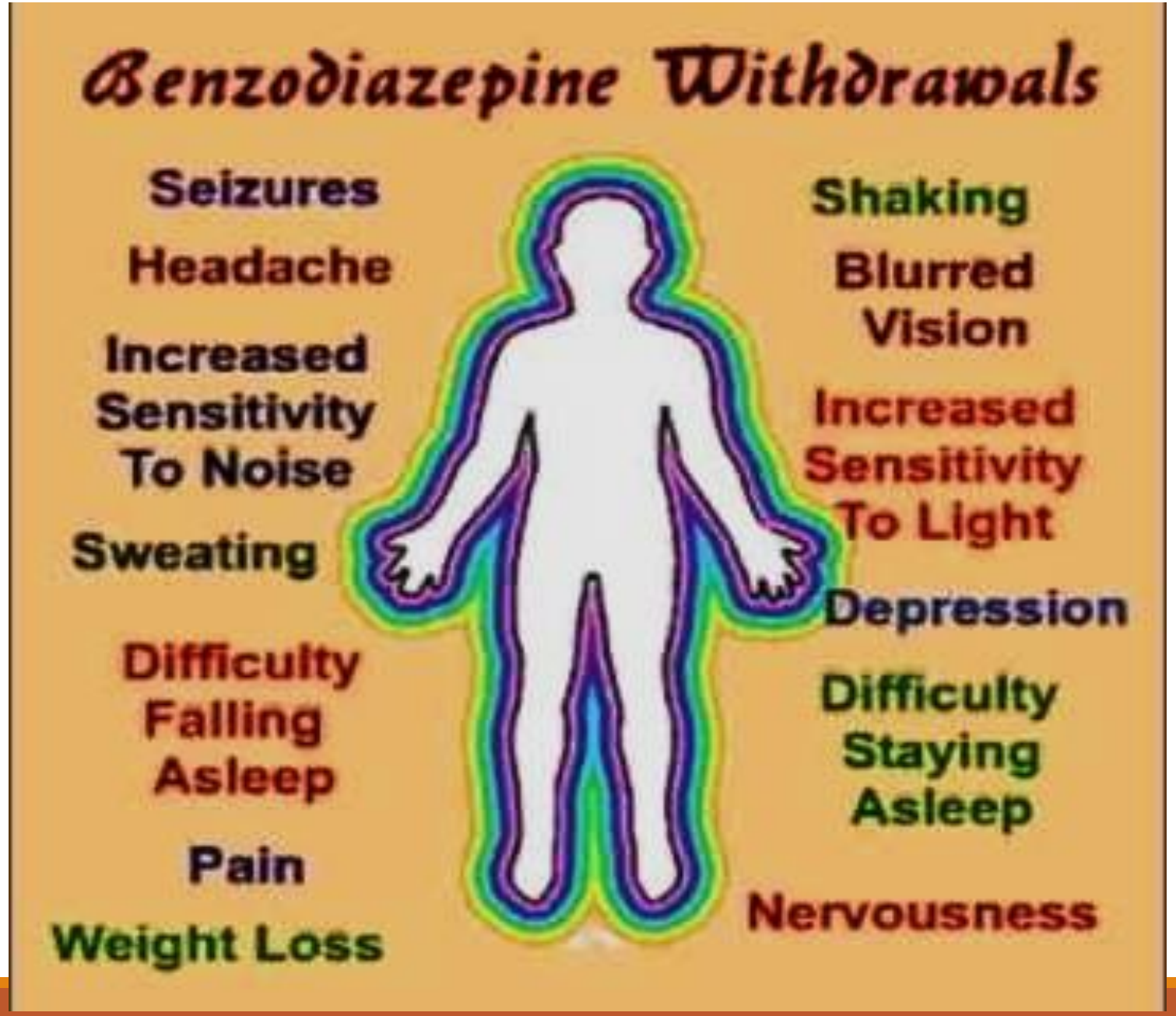
# Toxicity of Benzodiazepines

- Respiratory arrest is more likely with newer short-acting benzodiazepines such as triazolam (Halcion), alprazolam (Xanax), and midazolam (Versed). It has also been reported with zolpidem (Ambien).

- Cardiopulmonary arrest has occurred after rapid injection of diazepam, possibly because of CNS-depressant effects or because of the toxic effects of the diluent propylene glycol.

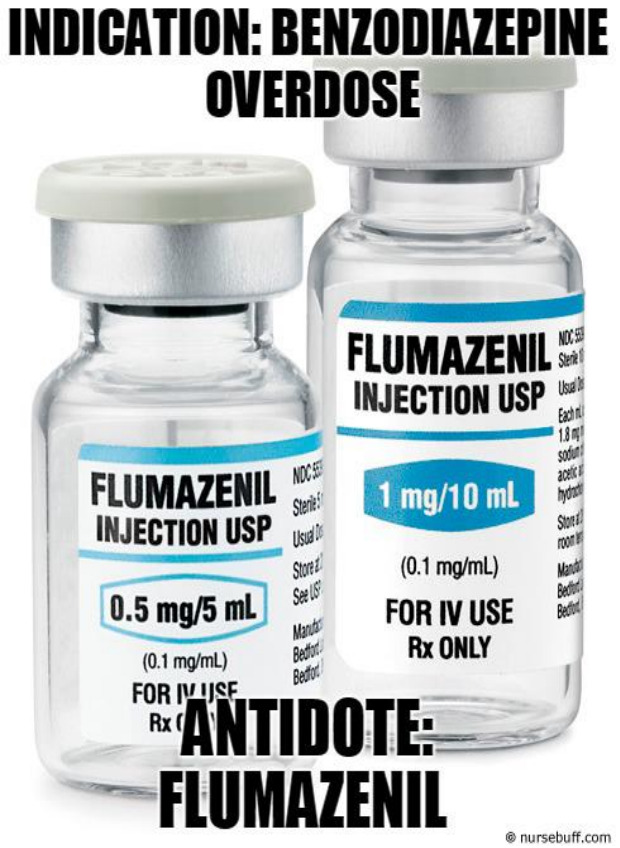
# Detection of Benzodiazepines

- Immunoassays are sensitive to the benzodiazepines that metabolize to oxazepam, (eg, diazepam, chlordiazepoxide, and temazepam), but may not detect newer benzodiazepines or those in low concentrations.


Benzodiazepine Withdrawals
Seizures
Headache
Increased Sensitivity To Noise
Sweating
Difficulty Falling Asleep
Pain
Weight Loss
Shaking
Blurred Vision
Increased Sensitivity To Light
Depression
Difficulty Staying Asleep
Nervousness

# Treatment of Benzodiazepines

- Flumazenil (1,4-imidazobenzodiazepine) : antidote
- Competitive benzodiazepine receptor antagonist
- Flumazenil completely reverses the sedative, anxiolytic, anticonvulsant, ataxic, anesthetic, comatose, and muscle relaxant effects

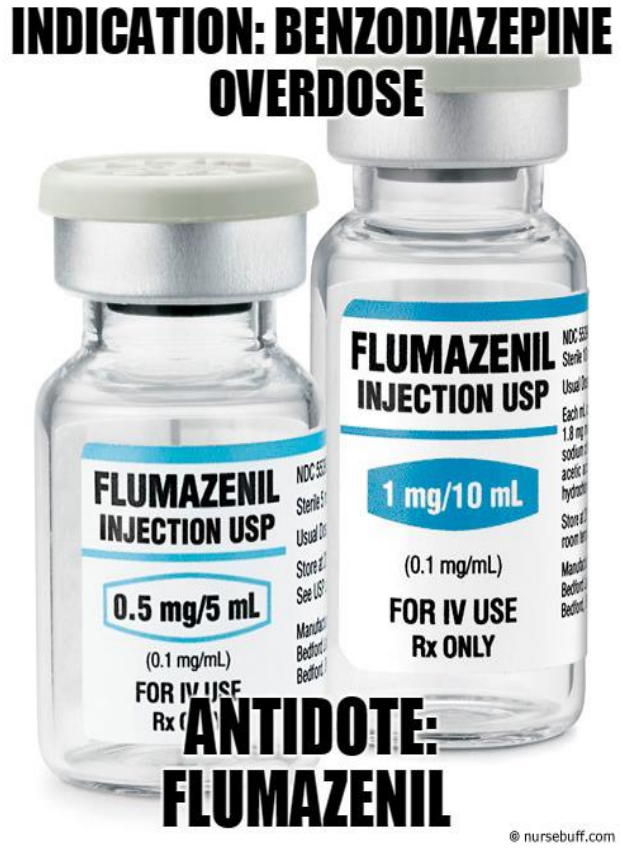


# Treatment of Benzodiazepines

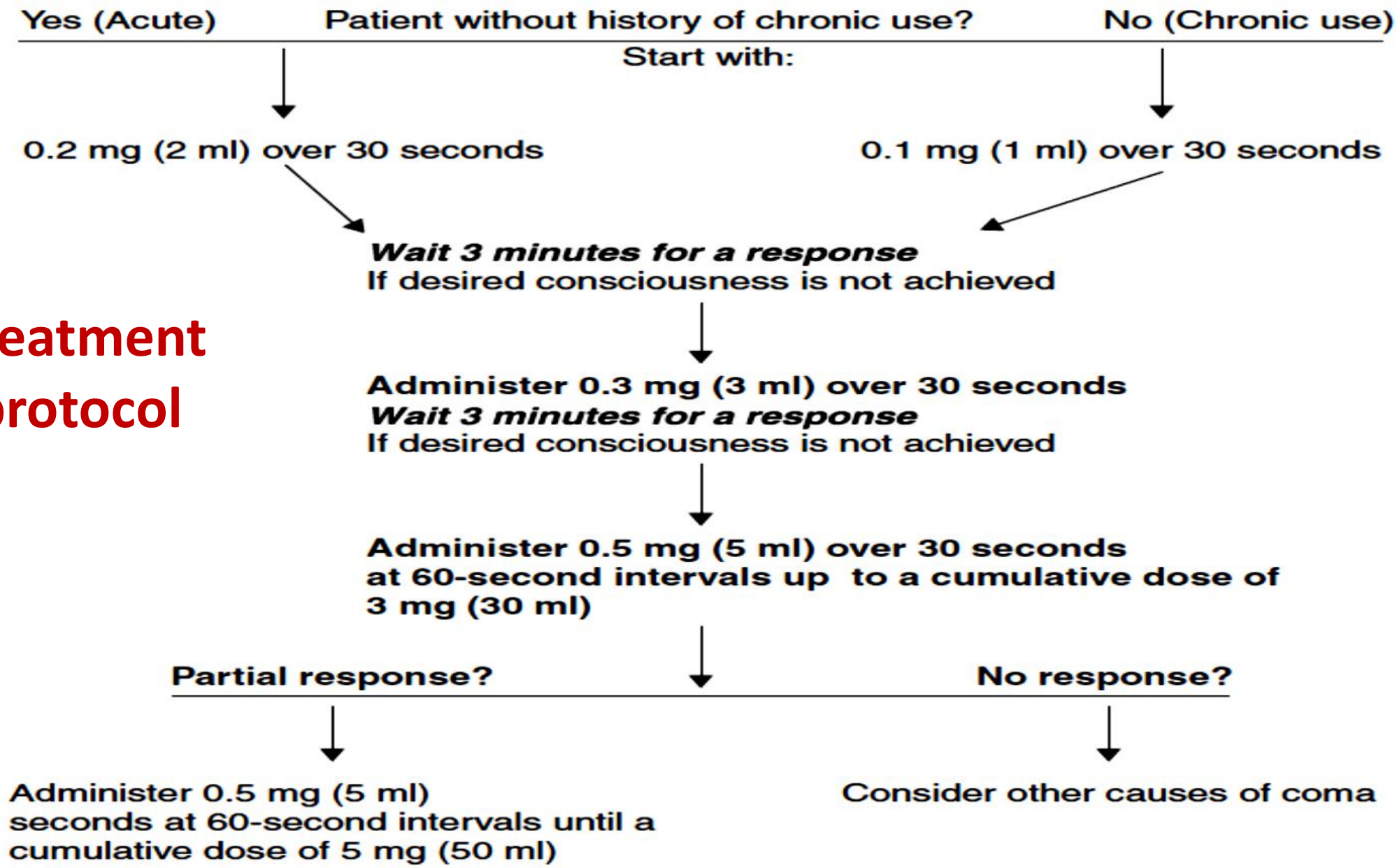
- Flumazenil dose = 0.2-1 mg i.v.
  Onset = 1-3 min
  Peak = 6-10 min

- It may induce acute withdrawal, including seizures and autonomic instability, in patients who are addicted to benzodiazepines

- Interaction with tricyclic antidepressant (TCA). May cause convulsions and produce ventricular arrhythmias



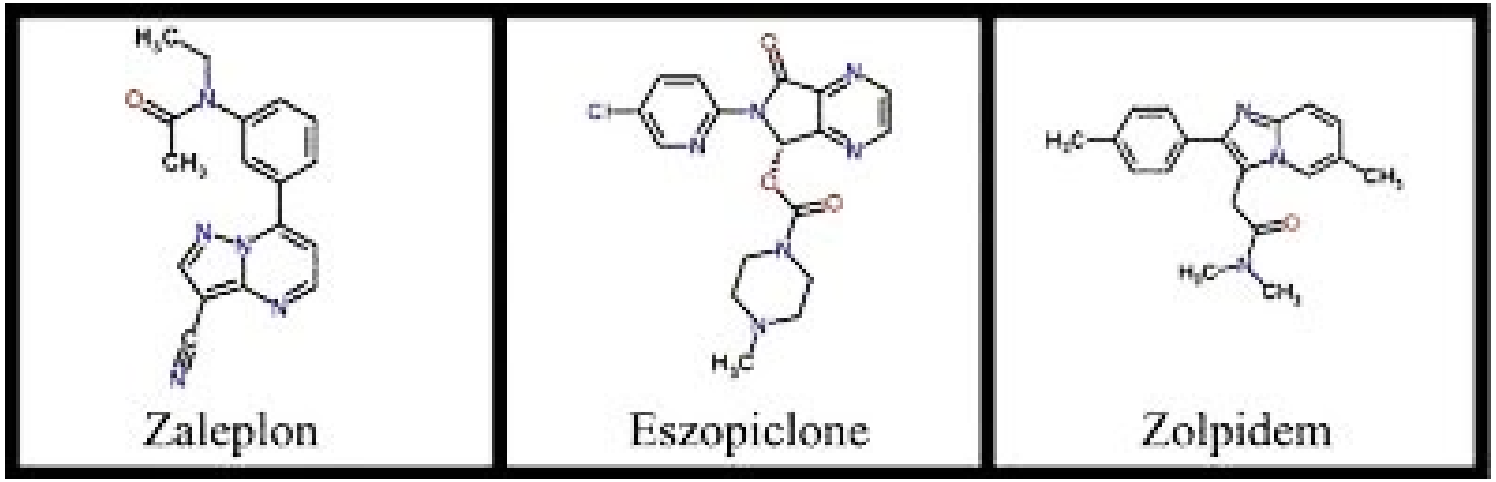
# Treatment protocol



| Barbiturates | Benzodiazepines |
| --- | --- |
| CNS depression | Concentrated effect |
| Sleep | Sleep comfort |
| Quick development of tolerance | Slow development of tolerance |
| Susceptible to dependence | Less susceptible to dependence |
| Drug-drug interaction | Less interaction |
| Low therapeutic index | High therapeutic index |
| No antidote | There is an antidote |

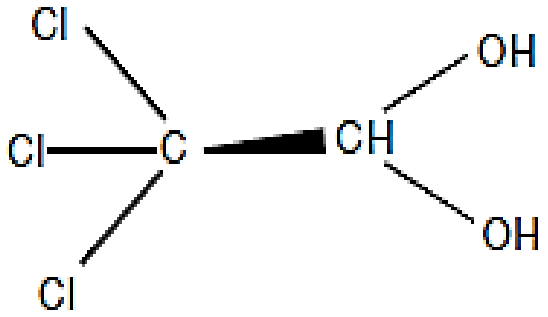
# Z drugs

- Similar to benzodiazepines
- Chemical structure : Pyrazolopyrimidines
- GABA A receptor agonist
- Short-acting



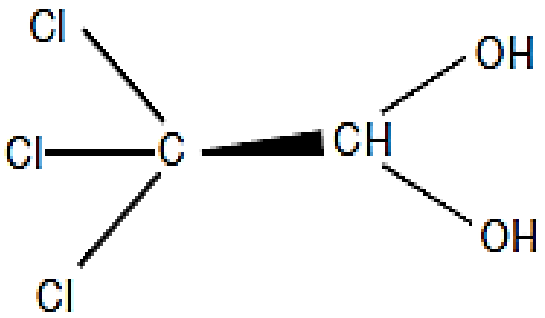

- Zolpidem , Zopiclone , Zaleplon

# Chloral hydrate




- It was introduced in 1832.
- It is only Hypnotic , and has no sedative effect.
- It is still used in children.
- Quick onset, Large distribution, rapid metabolism to **Trichloroethanol**
- **Trichloroethanol** is highly lipid soluble, and is responsible for the hypnotic effects
  - $t_{1/2}$ in plasma = 4-12 hours
- **Trichloroethanol** is responsible for the toxicity & low therapeutic index.

# Chloral hydrate




**Active metabolite**

Trichloroethanol

Conjugated with glucuronide

Urochloralic acid

Trichloroacetic acid

# Chloral hydrate

**Doses:**

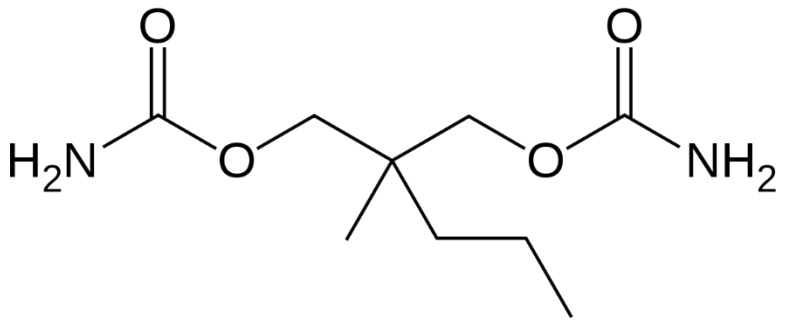
- Therapeutic does: 0.5-1 g.
- Therapeutic does for children : 50-75 mg/kg.
- Toxic does: 5-10 g

## Toxicity

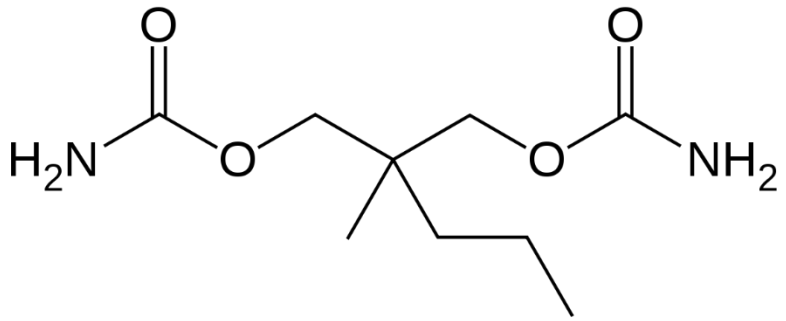
- Chloral hydrate cardiotoxic effects include lethal ventricular dysrhythmias, which is the major cause of death.
- β-adrenergic antagonists is recommended (such as propranolol)
- Chloral hydrate is irritating to the GI tract (vomiting, hemorrhagic gastritis, and rarely gastric and intestinal necrosis,

# Meprobamate

- It was introduced in 1955
- Carbamate derivative
- A metabolite of Carisoprodol
- anxiolytic and tranquilizer
- Anticonvulsant effect, muscle relaxant
- Its effects and risks are similar to barbiturates, susceptibility to addiction
- Currently a short-term treatment for anxiety




# Meprobamate





- أطلق عام 1955
- مشتق من الكاربامات Carbamate
- مستقلب للمرخي العضلي Carisoprodol
- مضاد للقلق anxiolytic ومهدئ tranquilizer
- تأثير مضاد اختلاج ,مرخي عضلي
- تأثيراته ومخاطره شبيهة بالباربيتورات , قابلية الإدمان
- حالياً علاج قصير الأمد للقلق

# Driving under the influence of alcohol (DUIA)

Dr.Samar Alzeer

# Driving is a complex process

- Motor tasks
- Hand-eye coordination
- Muscle control
- Make the right decision quickly
- Focusing attention on several things at once (distraction)

# Alcohol

- Slow neurotransmission
- Delayed reactions
- Inability to be distracted
- Cognitive and physical impairment

**CNS depressants**

Also, prescription medications such as sedatives, sedatives, muscle relaxants, and antidepressants.

**Other drugs:** cannabis, stimulants, hallucinogens

# Driving under the Influence

- Accident or reckless driving
- Notice signs of imbalance (imbalance checks)
- Check the level of alcohol in the breath at the scene of the accident
- Checking the blood alcohol level in the laboratory
- Transfer to court

### Stand on one leg test

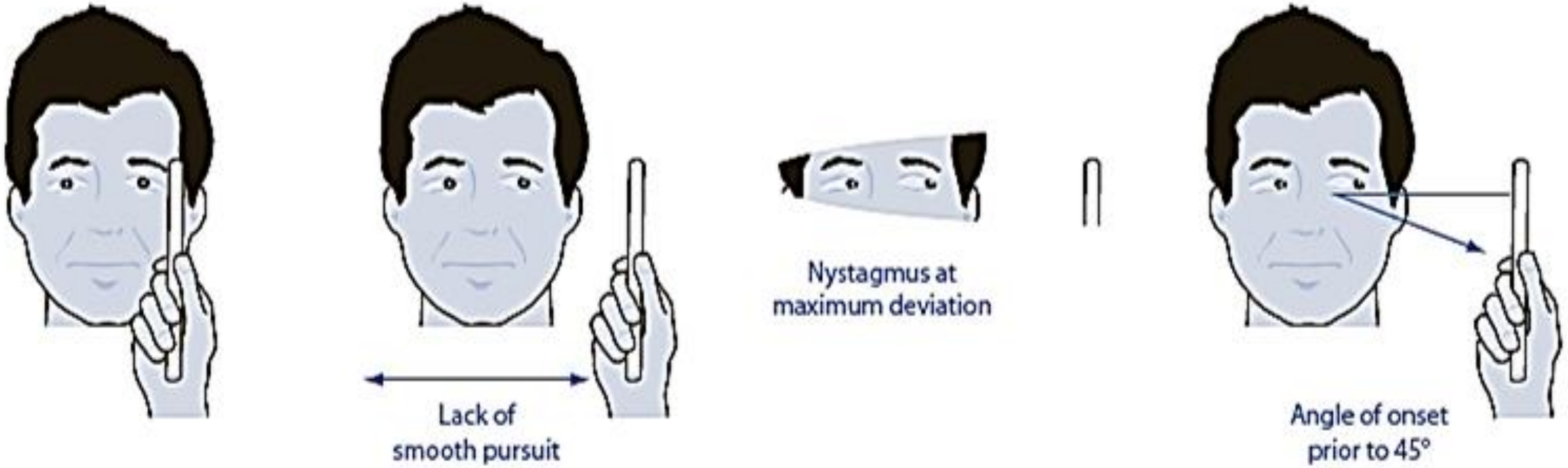
For this test the driver must raise the right foot six to eight inches off the ground and keep their hands by their sides.
They must then count 'one thousand and one, one thousand and two' and so on until the officer tells them to stop.
The officer checks whether the subject sways, hops, puts their foot down or raises their arms.

### Walk and turn test

The driver must walk along a real or imaginary line putting one foot directly in front of the other, heel to toe. They must take nine steps in this manner, counting out loud. When the ninth step has been taken they must leave the front foot on the line and turn around using a series of small steps with the other foot. After turning they must take another nine heel to toe steps along the line.

### Finger and nose test

The driver stands with feet together, hands out in front palms side up and closed with the index finger extended. The officer then asks the driver to tilt their head back and he then calls out a sequence of left and right commands and the driver must touch their nose with the corresponding index finger and then lower their head.

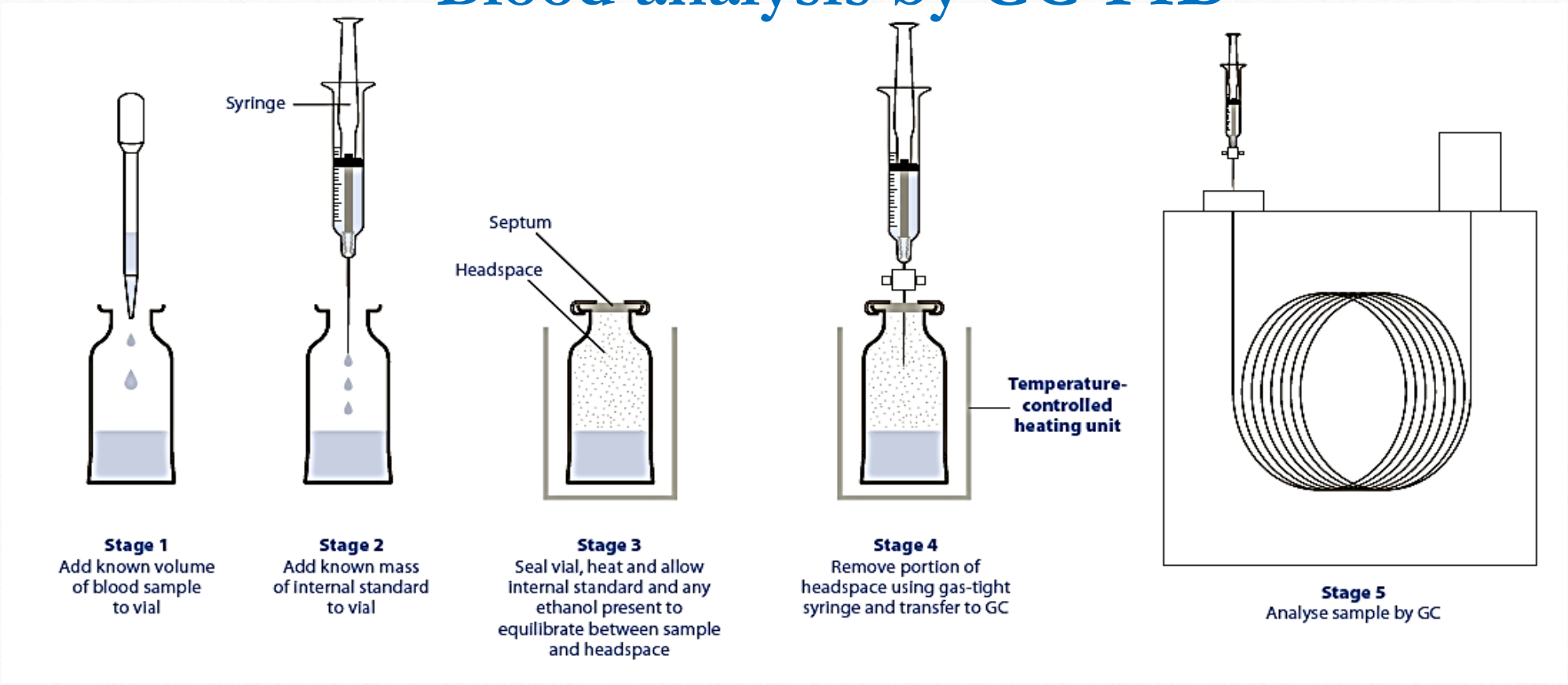



**Horizontal Gaze Nystagmus test**

An object is held in front of the driver's eyes. This is then moved to one side and then the other while the driver is asked to hold their head still and follow the movement of the object with their eyes. The officer observes the motion of the driver's eyes. If the driver is not impaired through drugs or alcohol their eyes should follow the object with a steady gaze. If they are impaired, the motion of the eyes will be jerky and the driver may have difficulty keeping their head still with a tendency to move the whole head in order to track the object.

# How to detect alcohol

## Blood analysis by GC-FID




Delay may affect results. Need specialists to take the sample

# How to detect alcohol

**Breath Alcohol content : 35 µg /100 ml**

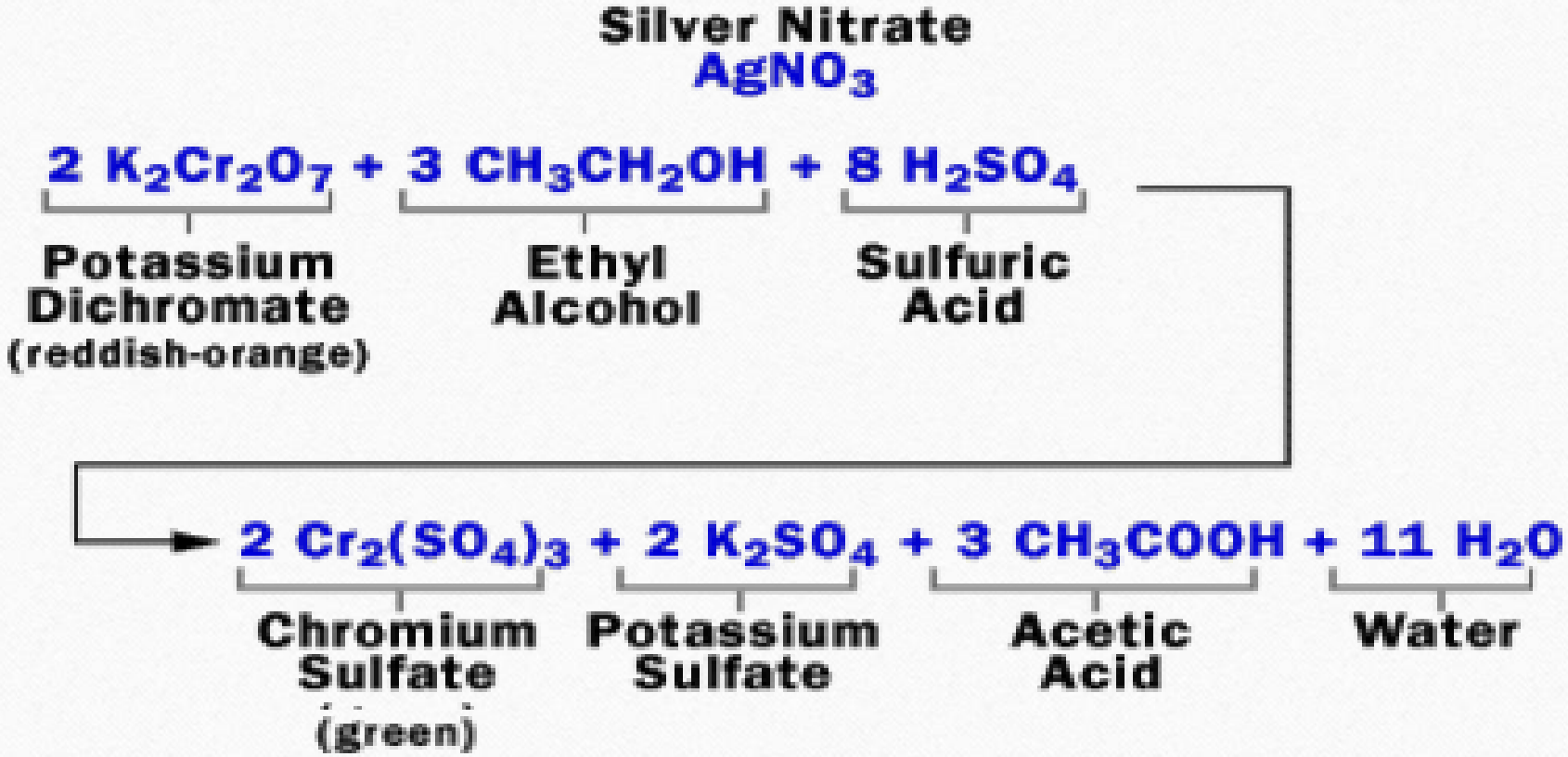
## Breath test

- Fast
- It does not require specialists or labs
- Sample collection is easy and painless
- Low cost

- Waiting 15 minutes after drinking to avoid false results (from oral alcohol)
- Read twice and use calibrators

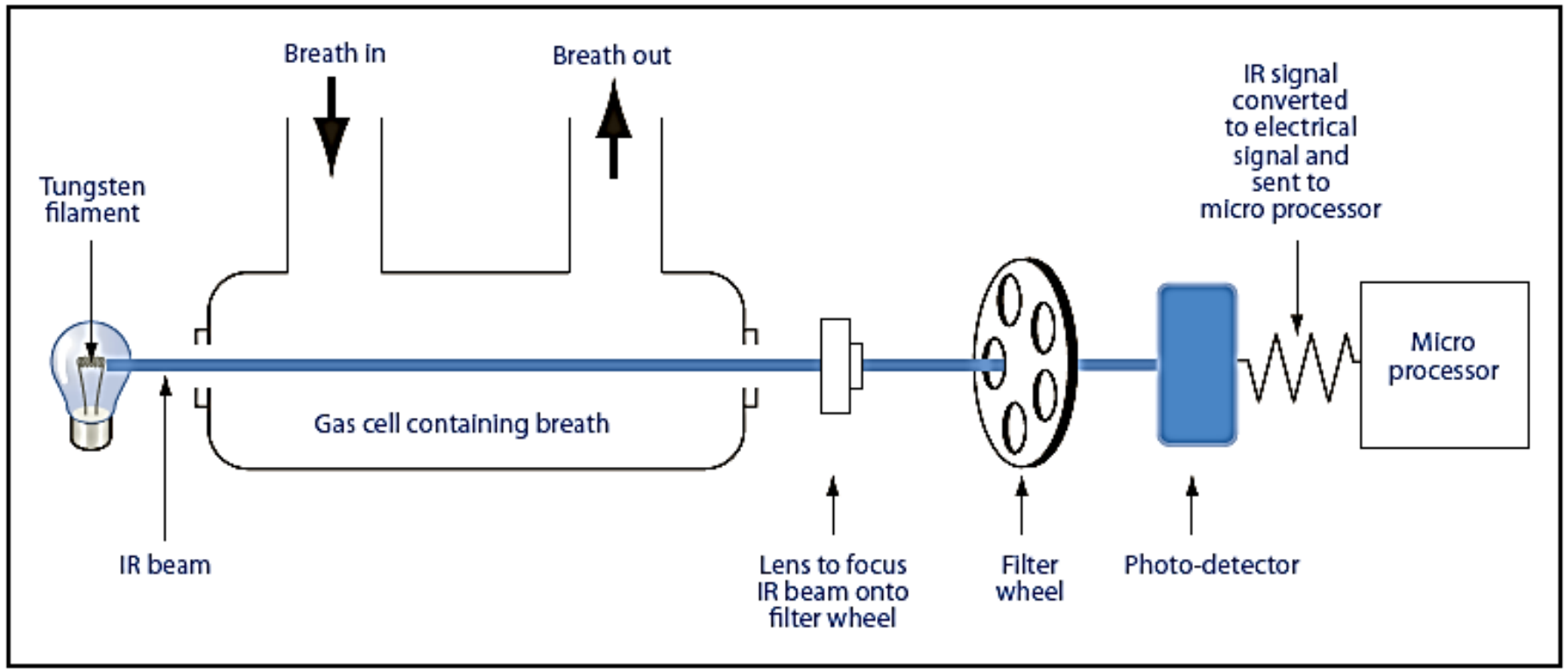
# How to detect alcohol

## Breath test



# How to detect alcohol- IR analysis

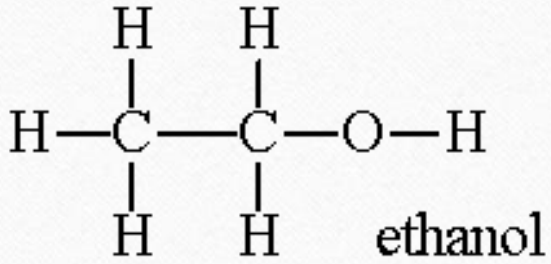
## Breath test




Alcohol
(beer, wine, liquor, whiskey, vodka, rum, gin)
Taken by drinking.

# Alcohol

- Ethanol is a CNS depressant
- ABV % (V/V or W/W)




## Alcohol production

**Fermentation only**: beer (4.5%) and wine (12%)

**Fermentation & Distillation**: vodka, whiskey, brandy and arak. Distillation increases the alcohol content in the drink by (40-60% ). called Spirit / Liquor

**Fermentation and the addition of distilled alcohol** (Fortified wines): sherry (brandy added). Adding distilled alcohol increases the alcohol content of the drink (20%)

# Alcohol

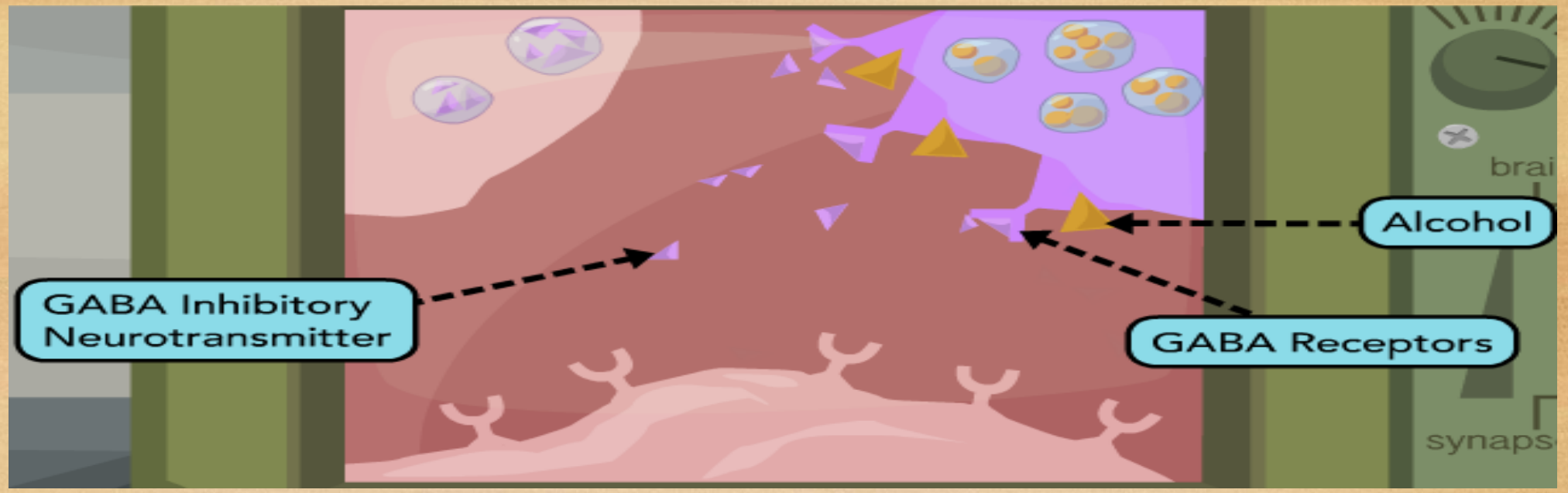
The **physiological effect** of alcohol depends on several factors:

- Concentration: the amount of alcohol consumed
- Time: Drinking alcohol feels more effective in the morning than in the evening
- Drinking rate: the same amount increases its effect when taken in a short period
- Tolerance: With time, the dose required to produce the same effect decreases
- Presence of other medications that increase CNS inhibition

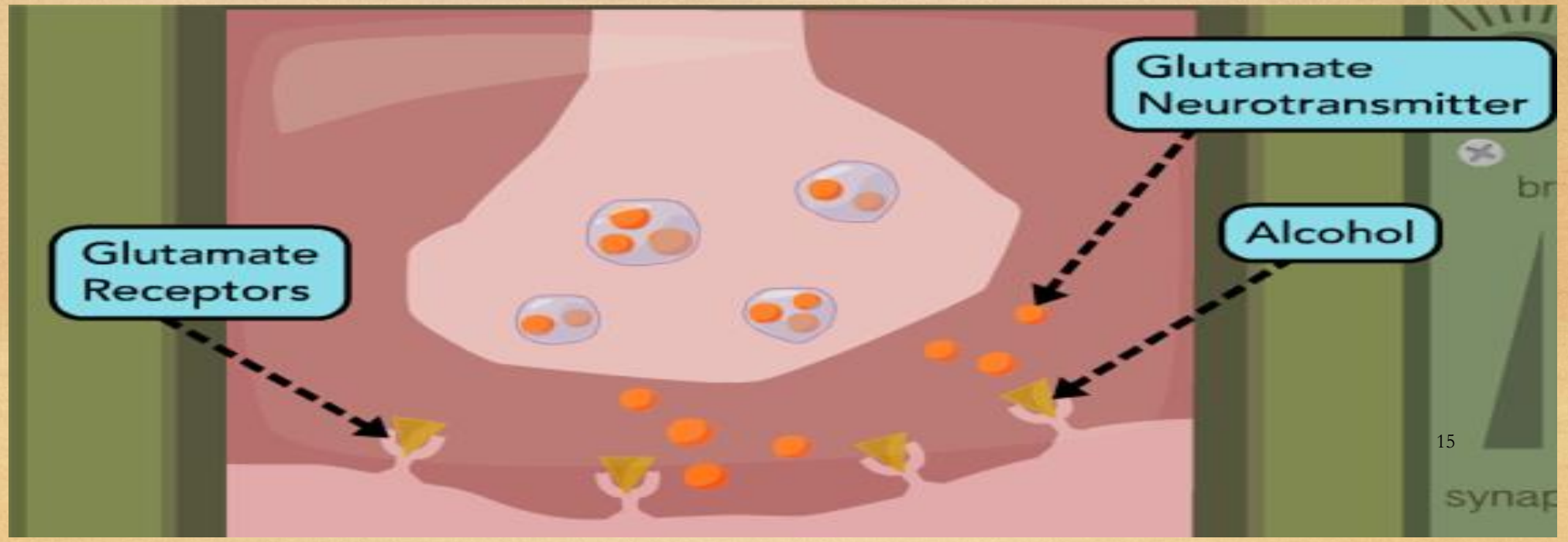
# Alcohol dose-effect relationship

| Alcohol concentration (mg/100 ml) | Physiological effect |
|---|---|
| Less than 50 | Increase speech |
| 50-100 | Difficulty speaking |
| 100-150 | Shaking , possibility of vomiting |
| 150-200 | Stupor, Vomiting |
| 200-300 | Coma |
| 300-450 | Possibility of death |
| More than 500 | Death |

1

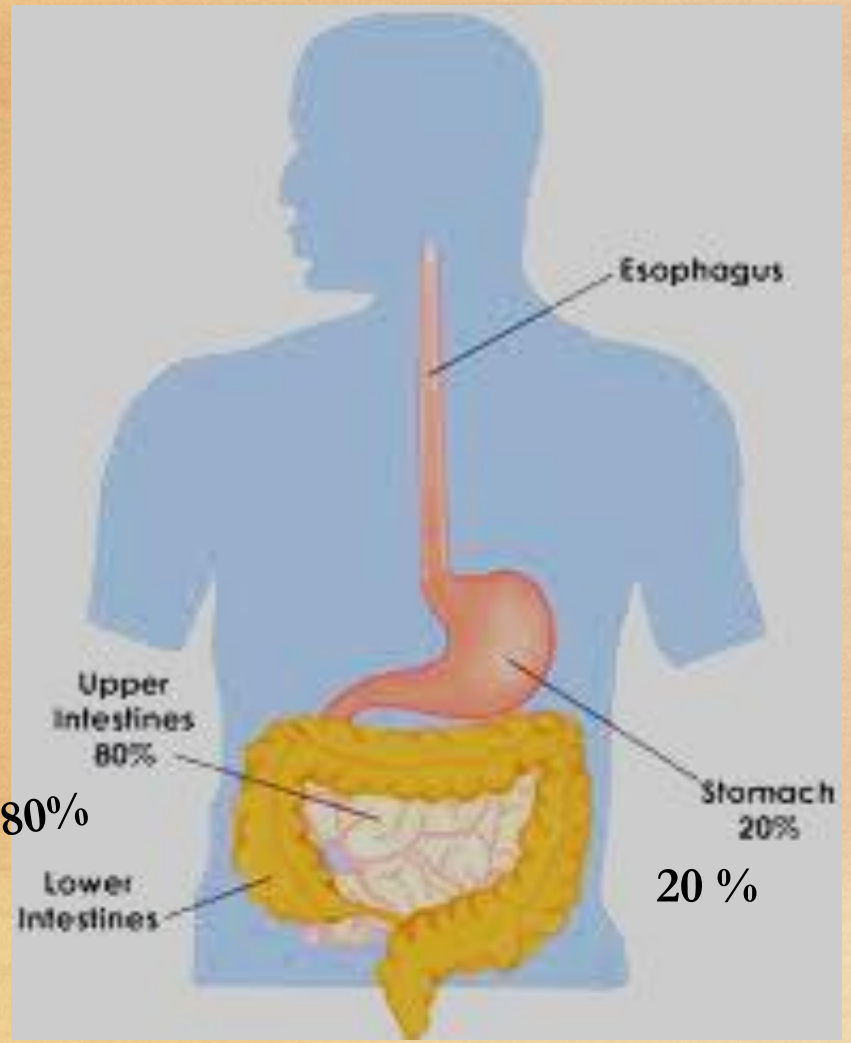

GABA Inhibitory Neurotransmitter
Alcohol
GABA Receptors

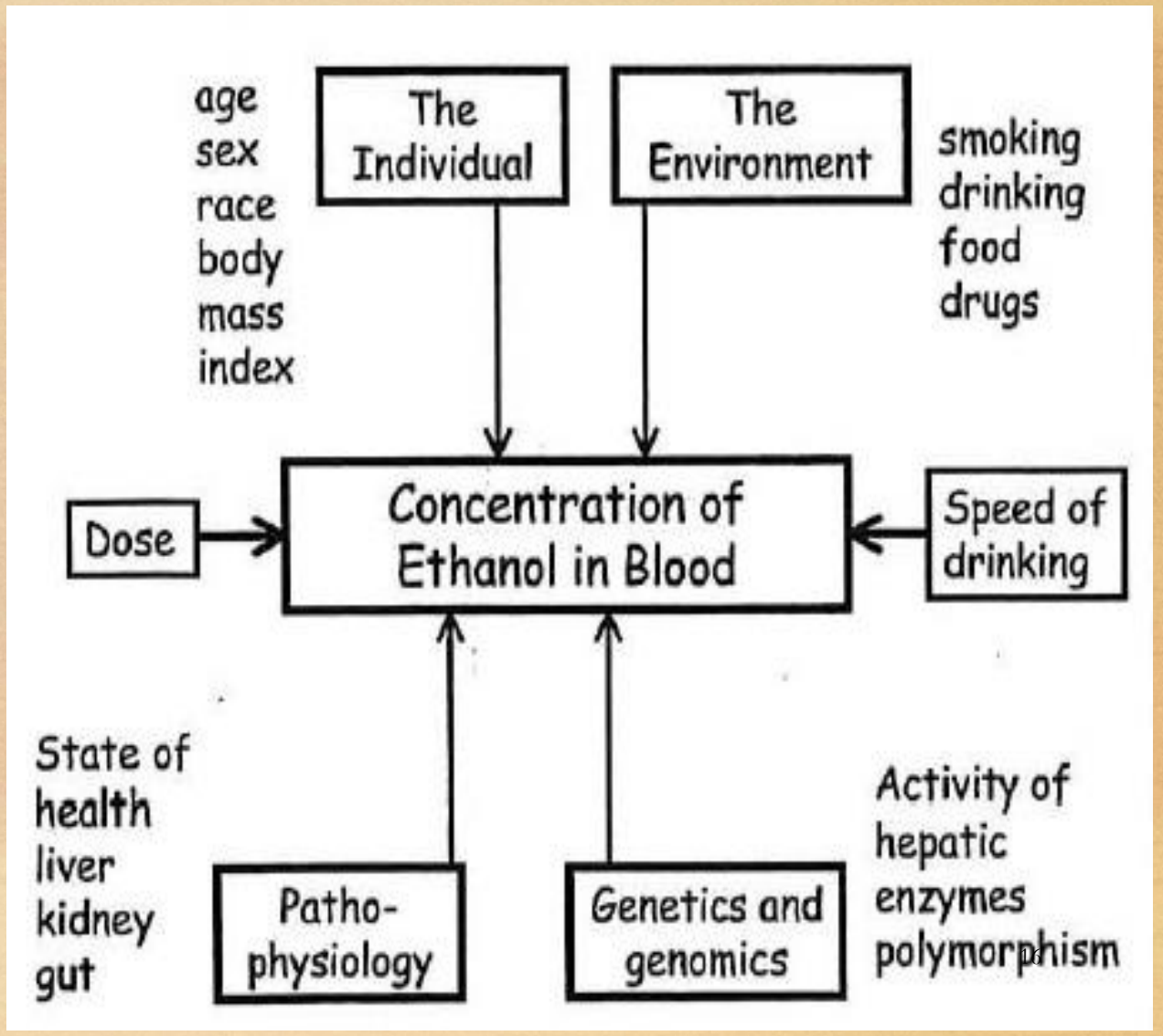
2


Glutamate Neurotransmitter
Glutamate Receptors
Alcohol

# Pharmacokinetics of Alcohol

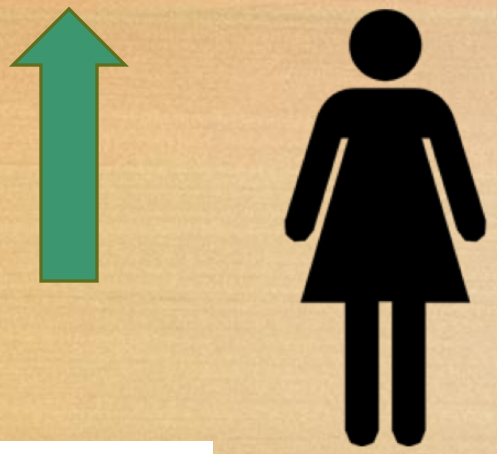
## Absorption

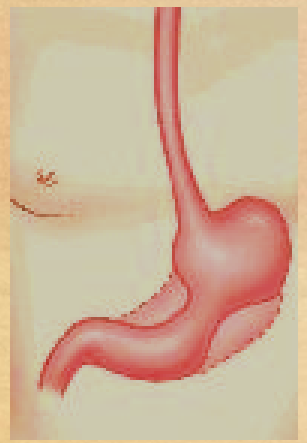


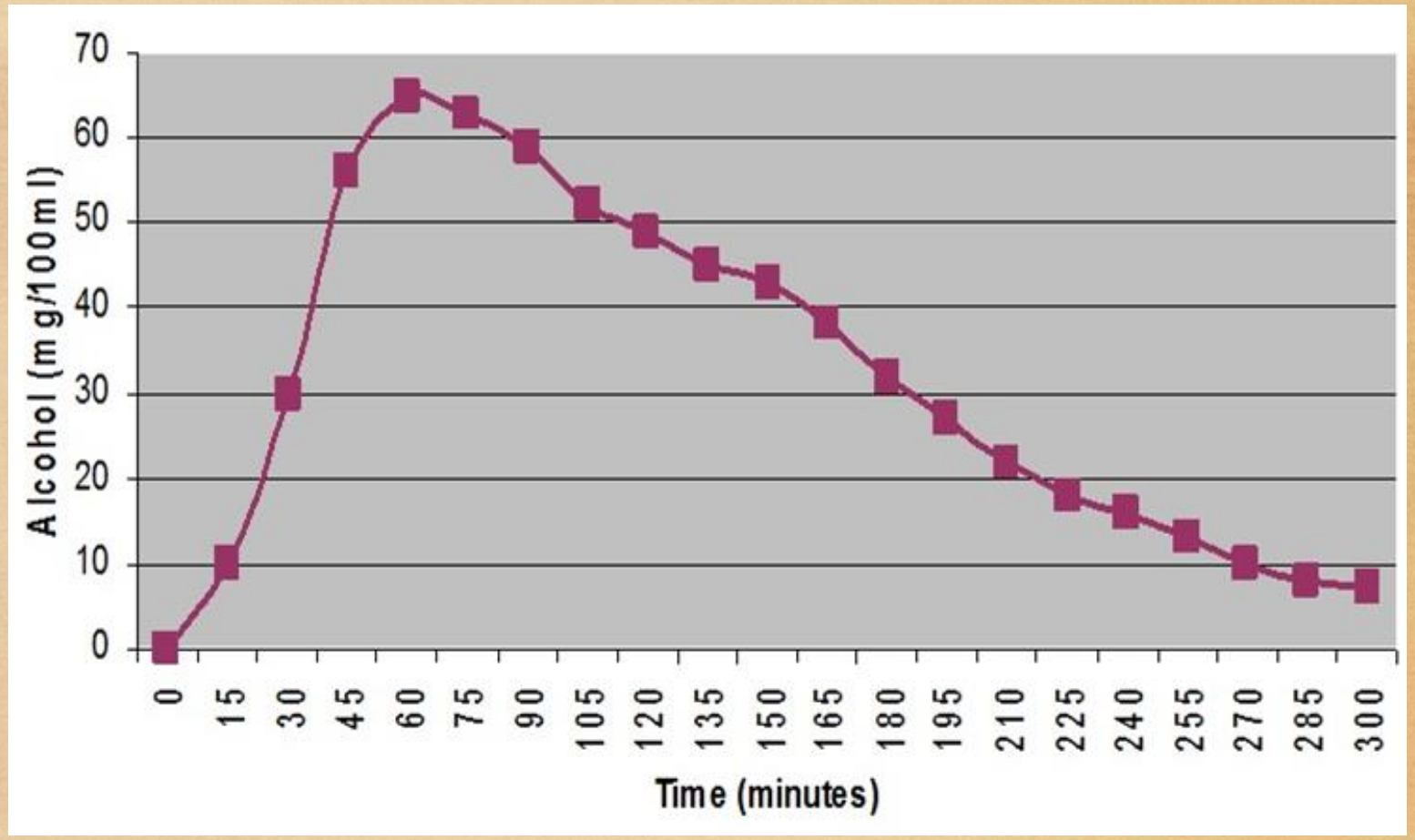



# Pharmacokinetics of Alcohol

## Absorption

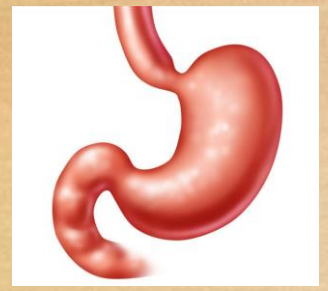




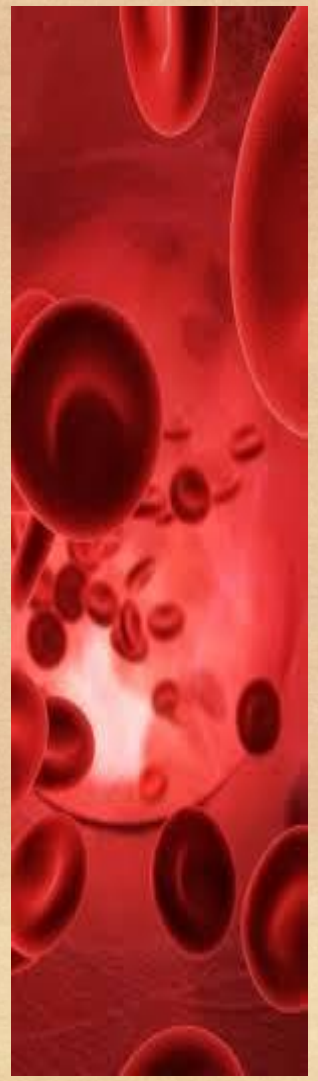


# Pharmacokinetics of Alcohol

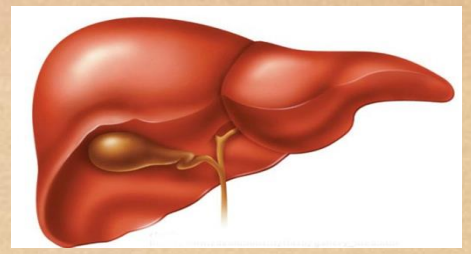
## Distribution

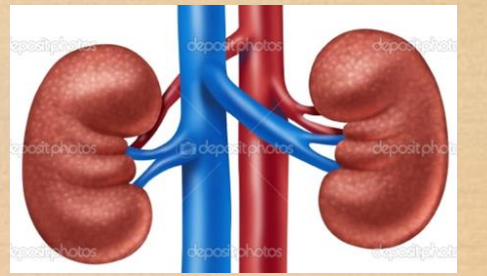


Alcohol

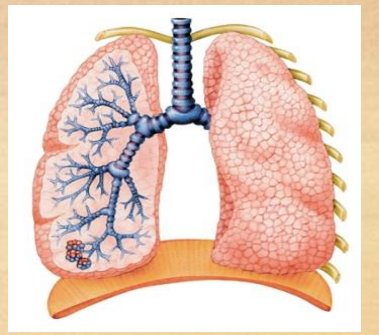


Body Water





Urine

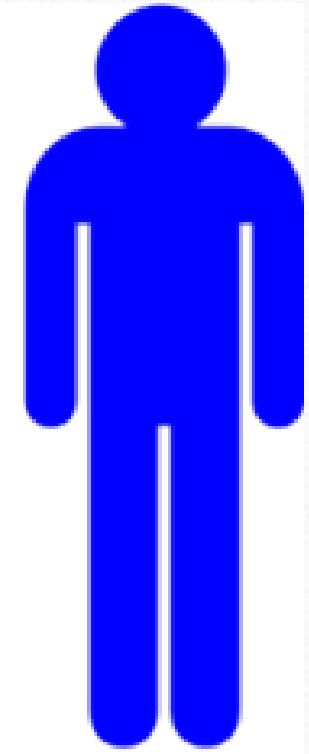


Breath

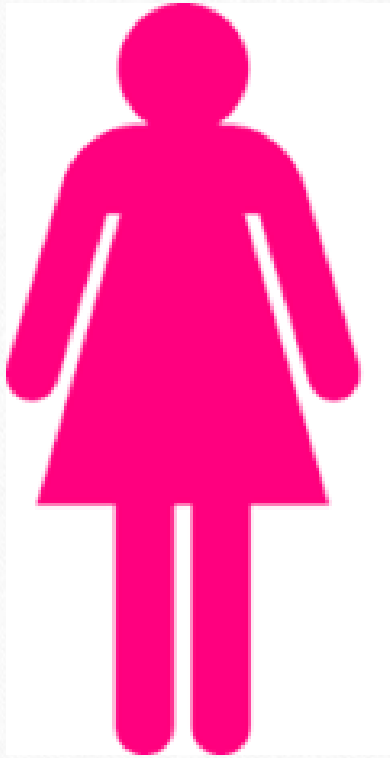
# Pharmacokinetics of Alcohol

## Distribution

Volume of distribution

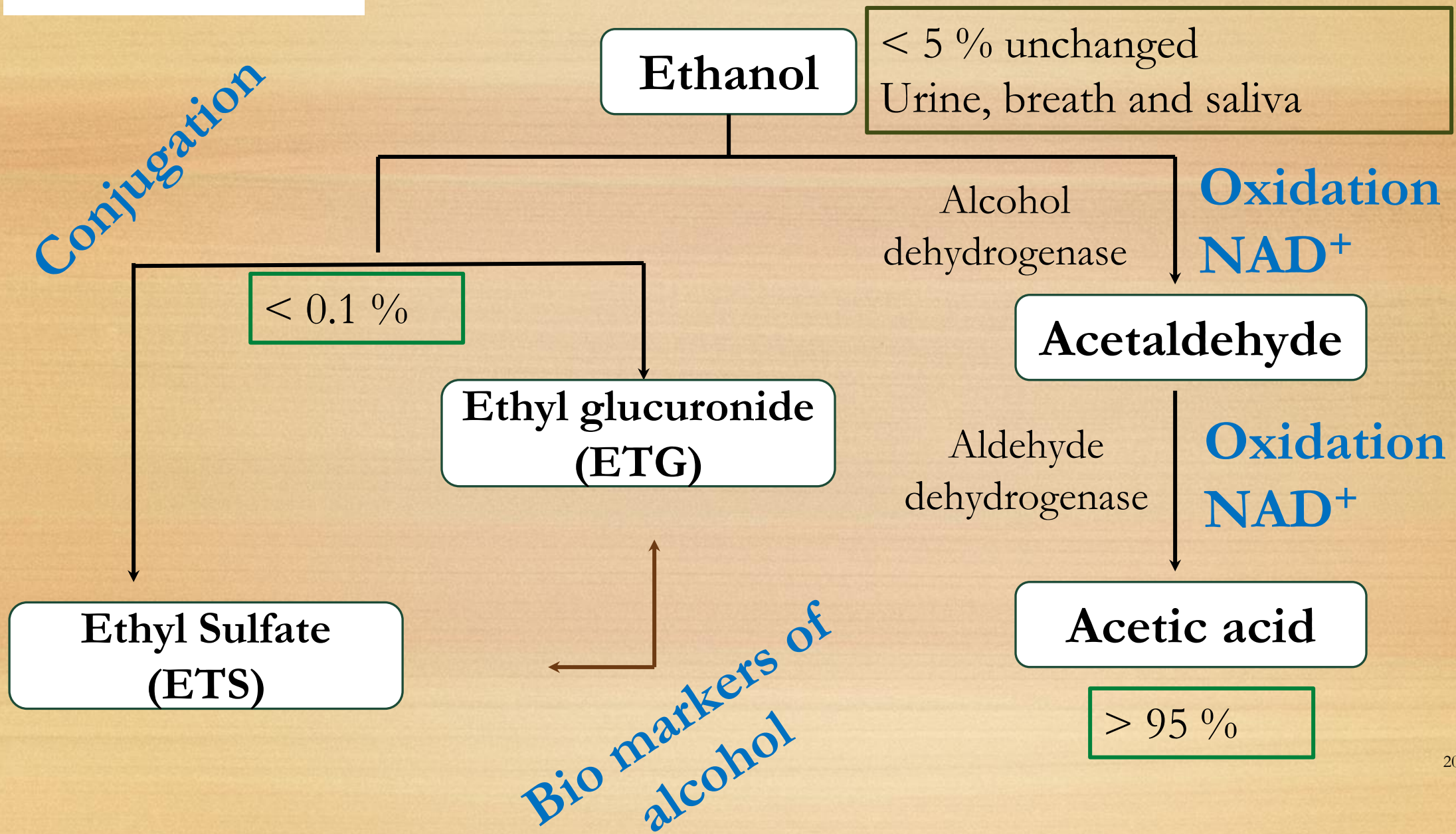


~ 68% of body mass



~ 55 % of body mass

# Metabolism


Ethanol
< 5 % unchanged
Urine, breath and saliva
Conjugation
< 0.1 %
Ethyl glucuronide (ETG)
Ethyl Sulfate (ETS)
Alcohol dehydrogenase
Oxidation NAD+
Acetaldehyde
Aldehyde dehydrogenase
Oxidation NAD+
Acetic acid
> 95 %
Bio markers of alcohol

# Pharmacokinetics of Alcohol

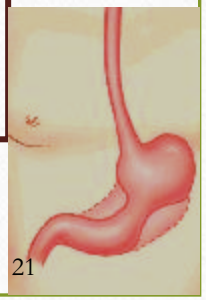
## Elimination

**Blood and urine alcohol clearance: mean 18-21 mg/100 ml/hour**
**(range: 9-27 mg/100 ml/hour)**

**Breath Alcohol clearance : 8 mcg/100 mL/hr**
**(range: 4-12 mcg/100mL/hr)**

Clearance rate is not related to concentration, and is not affected by sleep or muscular effort.
The rate of clearance increases with the presence of other drugs and with the occurrence of habituation.

Zero-order elimination



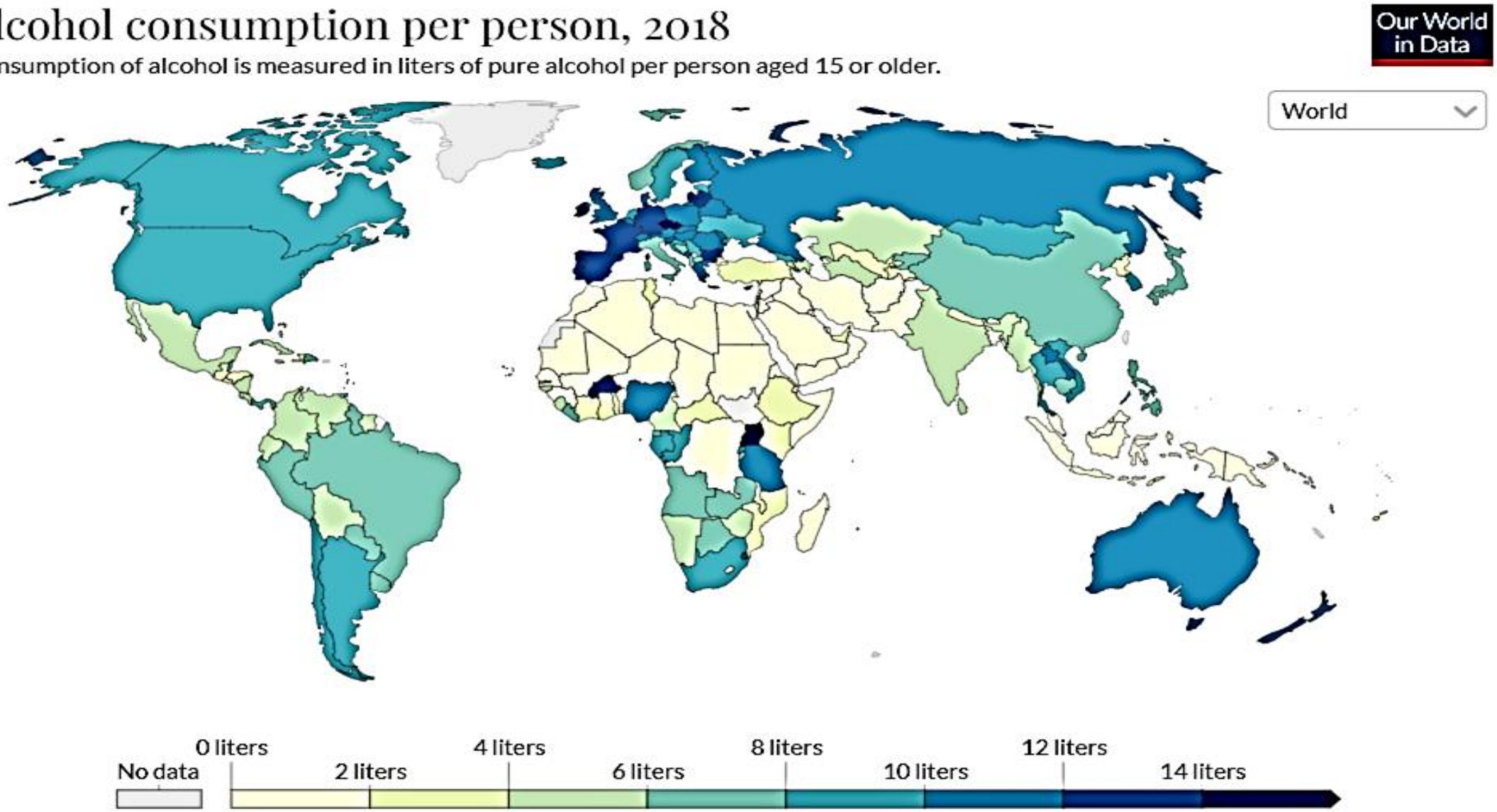
# Alcohol poisoning and death

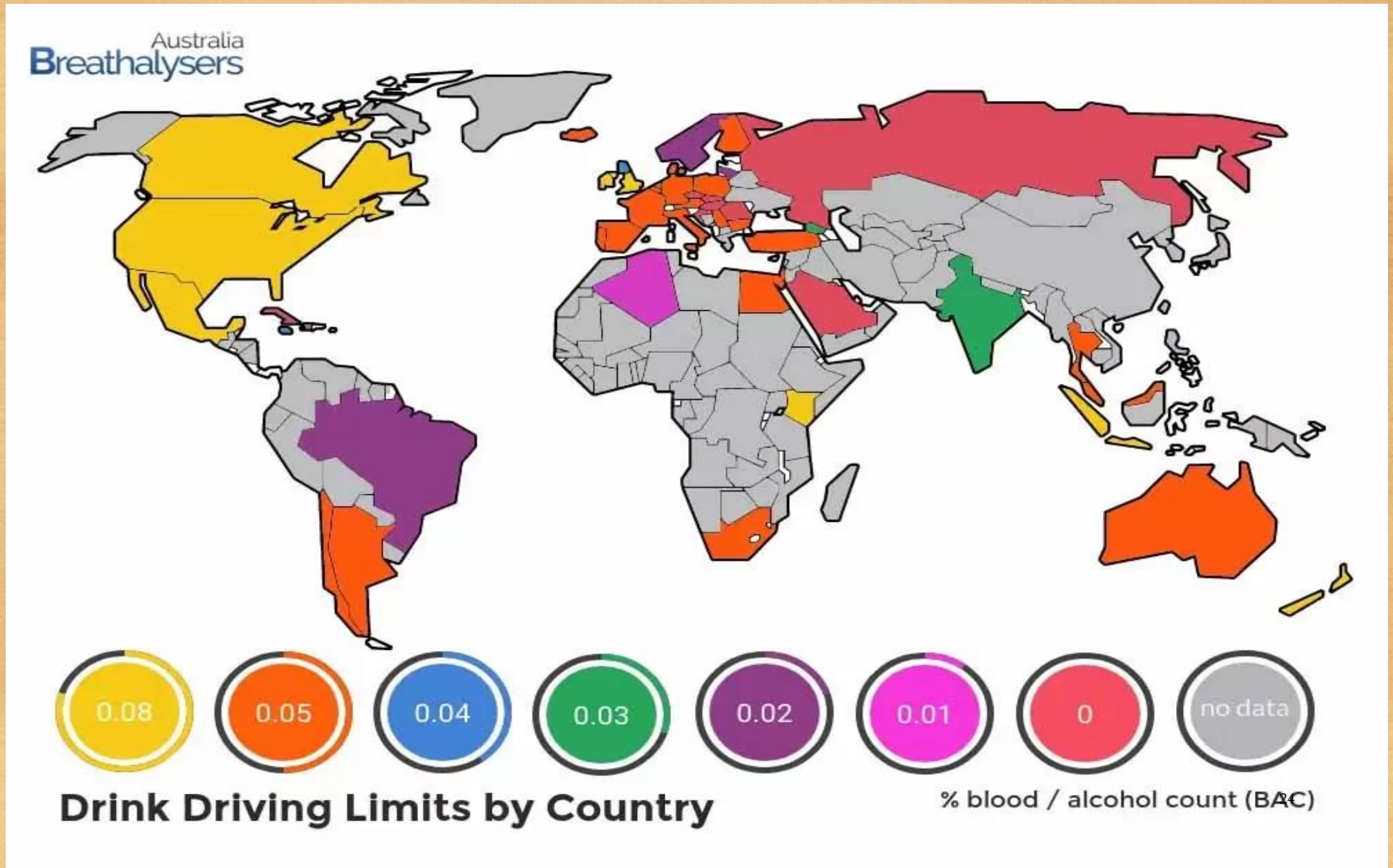
Alcohol is the third risk factor in developing countries after tobacco and hypertension, according to WHO

- Car accidents
- respiratory system depression
- Hypothermia
- Vomit entering the airway

# Alcohol consumption per person, 2018

Consumption of alcohol is measured in liters of pure alcohol per person aged 15 or older.




Australia
Breathalysers
0.08
0.05
0.04
0.03
0.02
0.01
0
no data
Drink Driving Limits by Country
% blood / alcohol count (BAC)

# Syrian Arab Republic

## ALCOHOL POLICY

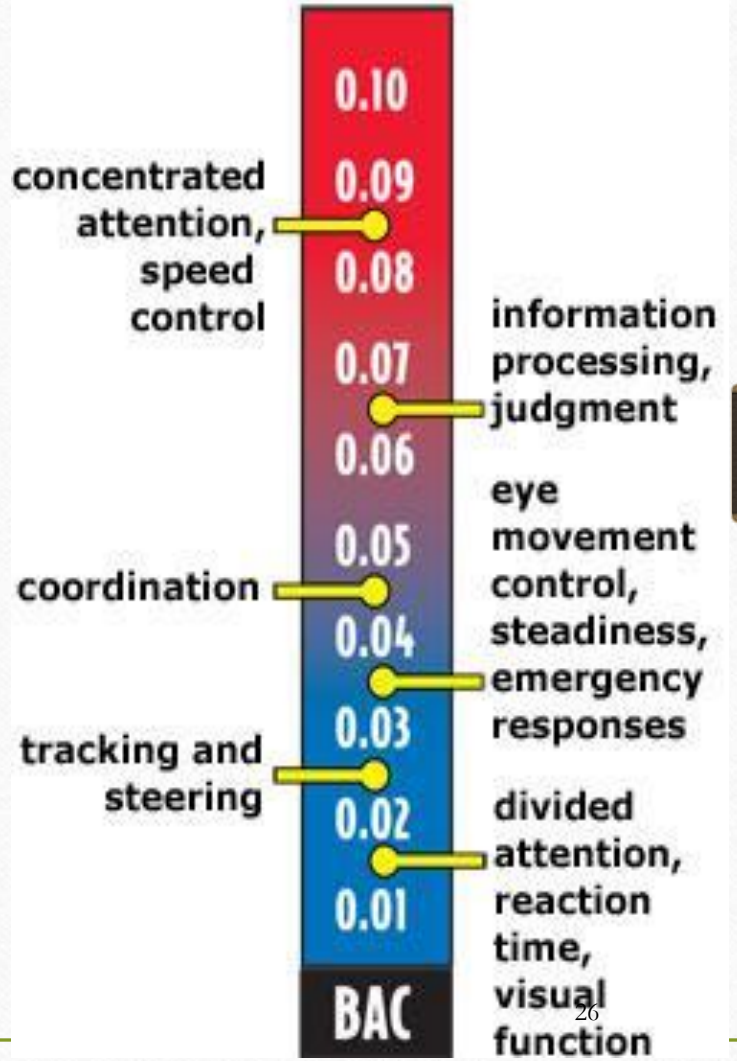
| | |
|---|---|
| Excise tax on beer / wine / spirits | NA |
| National legal minimum age for off-premise sales of alcoholic beverages (selling) (beer / wine / spirits) | NA |
| National legal minimum age for on-premise sales of alcoholic beverages (serving) (beer / wine / spirits) | NA |
| Restrictions for on-/off-premise sales of alcoholic beverages: | |
| Time (hours and days) / location (places and density) | NA |
| Specific events / intoxicated persons / petrol stations | NA |
| National maximum legal blood alcohol concentration (BAC) when driving a vehicle (general / young / professional), in % | 0.05 / 0.05 / 0.05 |
| Legally binding regulations on alcohol advertising / product placement | Total ban |
| Legally binding regulations on alcohol sponsorship / sales promotion | NA |

NA = No information.

# The maximum permissible limit of alcohol in the body

## Example : UK

- Blood Alcohol Content : 80 mg /100 ml (some countries 50 mg or less / 100 ml)
- Urine Alcohol content: 107 mg / 100 ml
- Breath Alcohol content : 35 µg /100 ml



# حساب كمية الكحول في الجسم

The following things must be known:

- When did the drinking happen?
- When did the driving accident happen?
- Analysis time
- Measured quantity
- What did the person drink? How many cups? Drink ABV concentration

**If alcohol concentration is measured directly**

**Dose (g) = Volume (ml) X Alcohol Concentration (%) X Density (0.78945 g/ml)**

**Time = concentration of alcohol to be eliminated / rate of elimination (excretion) of alcohol**

# دراسة حالة

A 22-year-old man was found by the police in his car at 2:35 am. Although he was asleep, the car was turned on. A breath test was conducted on the man and it gave a red result, which led to his arrest. He was given a breathing reaction at the police station with a more accurate device at exactly 03:15 am. His breath alcohol was 65 mcg/100mL of breathable air.

1- Was the percentage of alcohol in the man's breath above the permissible level?

2- What time can a man be allowed to drive his car?

# Case explanation

1- The maximum breath alcohol limit is 35 mcg / 100 ml. Therefore, the level of alcohol in a man's exhalation is higher than the permissible limit

2- The concentration was 65 mcg / 100 ml at exactly 03:15 am. The maximum permitted amount for driving is 35 mcg / 100 ml
Therefore, a man must excrete 30 mcg / 100 ml to be allowed to drive

**Time = concentration of alcohol to be eliminated / rate of elimination (excretion) of alcohol**

Breath alcohol clearance rate is 8 mcg/100mL/hr (range 4-12 mcg/100 mL/hr)

Average time = 30/8 = 3.75 hours = 3 hours and forty-five minutes
At the lowest rate of elimination, time = 30 / 4 = 7.5 = 7 and a half hours
At the highest rate of elimination, time = 12/30 = 2.5 hours = 2.5 hours

Therefore, a man can drive at 05:45 a.m. at least, 10:45 a.m., at most, or 07:00 a.m., on average.

# Calculating the amount of alcohol in the body

**When the percentage of alcohol was measured after a period of time, and an attempt was made to deduce the dose at the time of the accident**

1. Body Mass Index

$$BMI = \frac{w}{h^2}$$

Where:

w = weight of person (Kg)

h = height of person (M)

2. Percent fat

$$\%fat = a * BMI + b$$

Where a and b are constants whose value depend on gender and age

| | MEN | | WOMEN | |
|---|---|---|---|---|
| Age range (yrs) | a | b | a | b |
| 17 – 19 | 1.229 | -13.376 | 1.796 | -14.918 |
| 20 – 29 | 1.181 | -10.758 | 1.469 | -7.647 |
| 30 – 39 | 0.887 | 0.438 | 1.246 | 0.354 |
| 40 – 49 | 1.238 | -6.185 | 1.086 | 6.27 |
| 50 - 59 | 0.947 | 2.37 | 1.038 | 8.052 |

3. Widmark's factor 'r'

$$r = \frac{0.724\left(1 - \frac{\%fat}{100}\right)}{0.8}$$

4. Widmark's equation

$$C = \frac{d}{W * r * 10}$$

Where:

C = blood alcohol concentration in mg/100 mL

D = alcohol dose in mg

W = person's weight in Kg

r = Widmark factor

# Case study

A 50-year-old man. After dinner, he went to meet his friends and drank five glasses of alcohol (ABV = 5.2%, 330 ml) between seven and eight in the evening. He drove his car and at 10:10 pm , he caused a car accident.

He came home and to forget what happened, he drank two glasses of vodka (each glass is 35 ml, ABV=40%).

The police arrived at 10.53 p.m. and measured his breath alcohol concentrations at 11:41 p.m. It was 64 ug/100 ml.
Since the weight of a man is 82.6 kg and that his height is 1.78 cm, Calculate the percentage of alcohol in his body at the time of the accident.
Was it above normal?
When is he allowed to drive?

# Case explanation

$$BMI = \frac{W}{h^2} = \frac{82.6}{(1.78)^2} = \mathbf{26.1}$$

**BMI calculation**

| | MEN | | WOMEN | |
|---|---|---|---|---|
| Age range (yrs) | a | b | a | b |
| 17 – 19 | 1.229 | -13.376 | 1.796 | -14.918 |
| 20 – 29 | 1.181 | -10.758 | 1.469 | -7.647 |
| 30 – 39 | 0.887 | 0.438 | 1.246 | 0.354 |
| 40 – 49 | 1.238 | -6.185 | 1.086 | 6.27 |
| 50 - 59 | 0.947 | 2.37 | 1.038 | 8.052 |

$$\%\, fat = a * BMI + b = (0.947)(26.1) + 2.37$$
$$= \mathbf{27.1}\ \%$$

**Calculation of % fat**

# Case explanation

Widmark factor

$$r = \frac{(0.724)(1 - {}^{\%\,fat}/_{100})}{0.8}$$

$$= \frac{(0.724)(1 - {}^{27.1}/_{100})}{0.8} = \mathbf{0.66}$$

$$Dose_{VODKA} : \sum volume * \frac{ABV}{100} * 0.78945$$

$$= 2\ x\ 35\ x\ \frac{40}{100}\ x\ 0.78945 = 22.105\ g$$

$$\equiv \mathbf{22105\ mg}$$

$$BAC_{VODKA} : \frac{Dose}{W * r * 10} = \frac{22105}{82.6 * 0.66 * 10}$$

$$= \mathbf{40.55\ mg\ /100\ mL}\ Blood$$

Calculating the dose of vodka after the accident

# Case explanation

$35\ \mu g/100mL\ \equiv 80\ mg/100\ mL$

Converting breath concentration to blood concentration

$$64\ \mu g/100mL\ \equiv \frac{64\ x\ 80}{35}$$

$$= \mathbf{146.29\ mg/100\ mL}\ Blood$$

**The true concentration in the blood without calculating the post-accident vodka**

$$Measured\ level - vodka$$

$$= 146.29 - 40.55$$

$$= \mathbf{105.74\ mg/100\ mL}\ Blood$$

# Case explanation

**Elimination time**

Elimination since the incident: 10.10 – 11.41 = 1h 31min ≡ 1.52 h

$$Slow:\ 9\ mg/100\ mL/h\ *1.52\ h\ =\ \mathbf{13.68\ mg/100\ mL}$$
$$Avg:\ 18\ mg/100\ mL/h\ *1.52\ h\ =\ \mathbf{27.36\ mg/100\ mL}$$
$$Fast:\ 27\ mg/100\ mL/h\ *1.52\ h\ =\ \mathbf{41.04\ mg/100\ mL}$$

**Concentration in the blood at the time of the accident**

Therefore, BAC @ time of incident:

$$105.78 + \begin{pmatrix} 13.68 \\ 27.36 \\ 41.04 \end{pmatrix} = \begin{matrix} \mathbf{119.46} \\ \mathbf{133.14}\ \mathbf{mg/100\ mL} \\ \mathbf{146.82} \end{matrix} \begin{matrix} Slow \\ Avg \\ Fast \end{matrix}$$

# Case explanation

- $64 - 35 = \mathbf{29\ \mu g/100\ mL}$

$$29 \div \begin{pmatrix} 4 \\ 8 \\ 12 \end{pmatrix} \mu g/100\ mL/h$$

$$= \begin{pmatrix} 7.25 \\ 3.63 \\ 2.42 \end{pmatrix} h$$

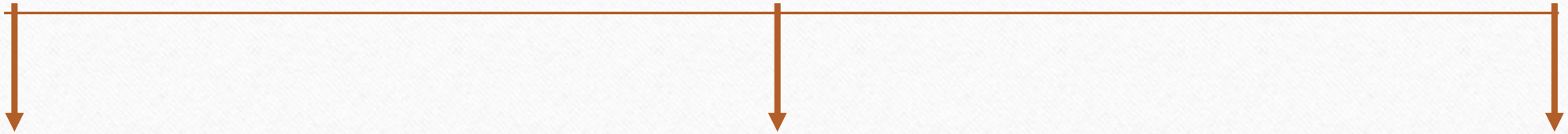
**When is he allowed to drive?**

11.41 pm + 7h 15min = **6.56 am**
11.41 pm + 3h 38min = **3.19 am**
11.41 pm + 2h 25min = **2.23 am**

# Pesticides

Dr. Samar Alzeer

# Pesticides



Insecticides

Rodenticides

Herbicides

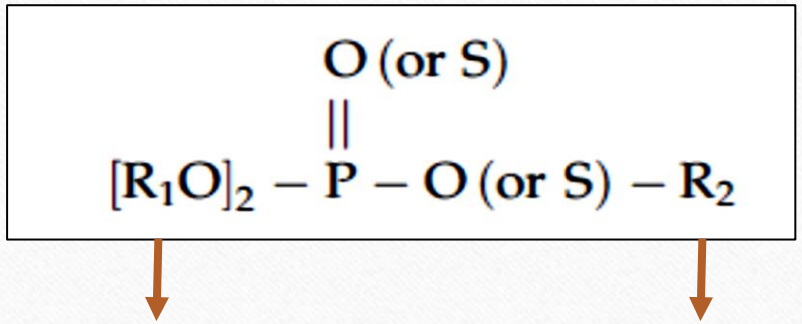
# Insecticides

- **Cholinesterase inhibitors**
  - Organophosphorus compounds (OP)
  - Carbamates
- **Organochlorine compounds (OC):** DDT, cyclodienes, lindane
- **Pyrethroid Esters**: pyrethrins type I and II
- **Other insecticides** : Nicotine , Boric acid, Rotenone, Diethyltoluamide (DEET)

# Insecticides

## Organophosphorus compounds (OP)

- **Tetraethyl pyrophosphate (TEPP):** Most potent OP
- **Chlorpyrifos**
- **Malathion** : high commercial value
- **Dimethoate** : contains sulfur and requires metabolic activation



# Insecticides

## Organophosphorus compounds (OP)

- First developed as nerve gases during world war II
- Household and agricultural insecticides.
- Suicide attempts

50-70% of deaths in developed world

- most rapidly absorbed after inhalation, especially

when delivered in aromatic hydrocarbon vehicle solvents

**Exposure routes**

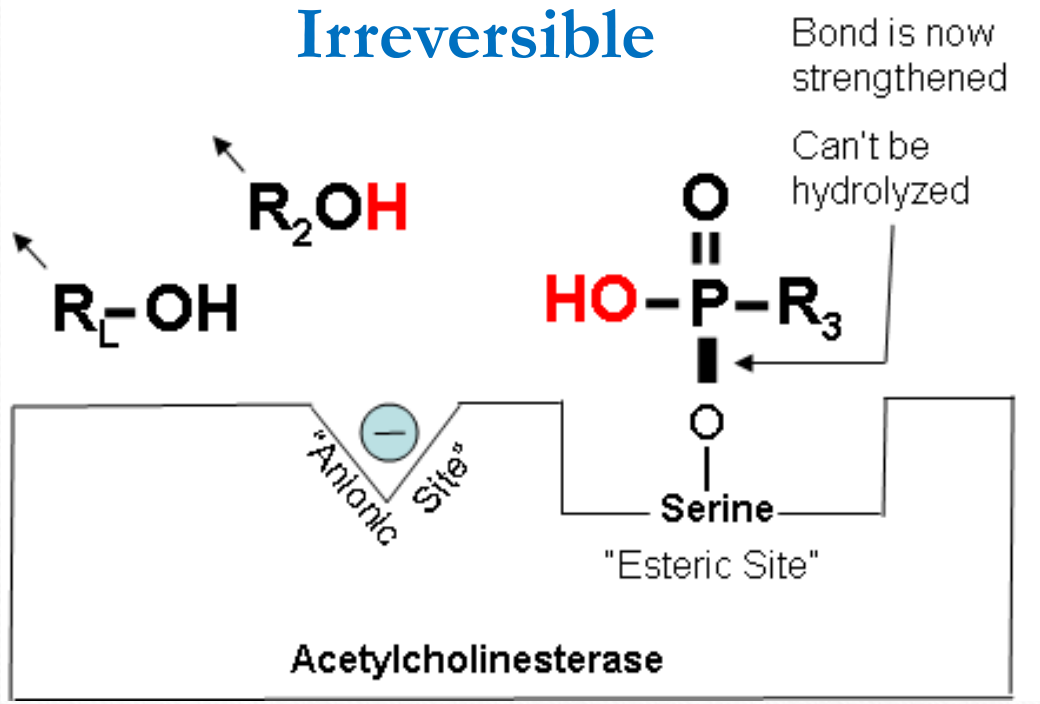
- ❖ Oral ingestion
- ❖ Inhalation
- ❖ Dermal contact

# Insecticides

## Organophosphorus compounds (OP)

### Mechanism of Toxicity

- Irreversible inhibition of acetylcholinesterase
- Accumulation of acetylcholine
- Takes days to weeks for disassembly



# Insecticides

## Organophosphorus compounds (OP)

### Mechanism of Toxicity

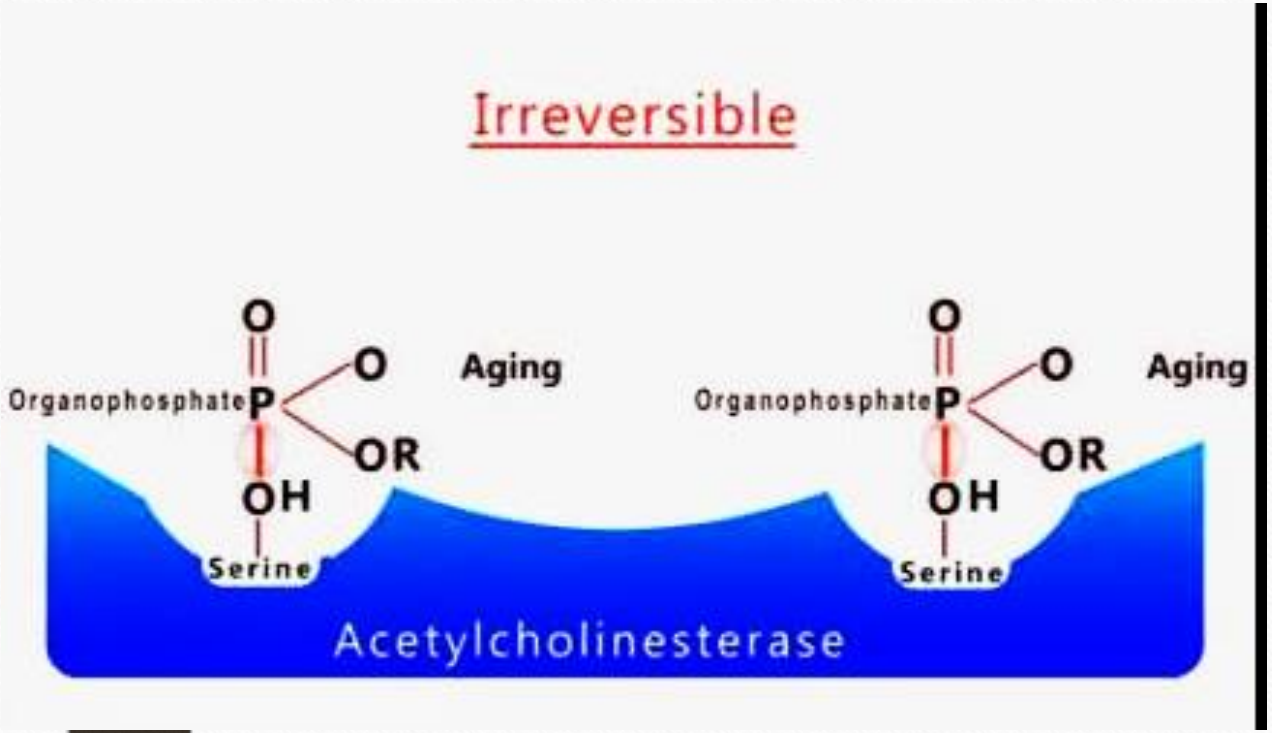
Enzyme undergoes (Aging) process

↓

Loses an alkyl group

↓

Does not regenerate



# Organophosphorus compounds (OP)

- **Acute Toxicity**

## Cholinergic muscarinic stimulation

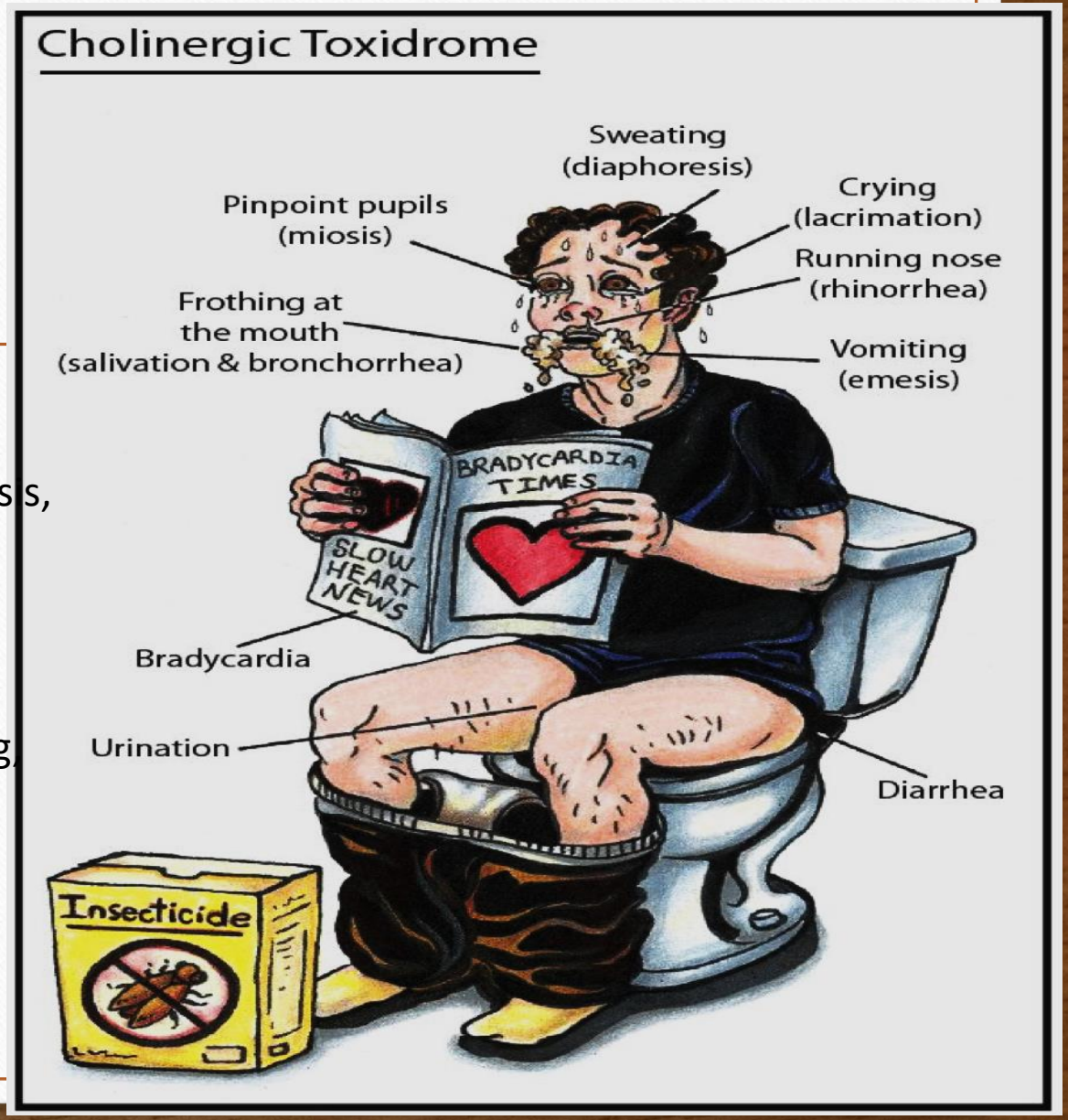
salivation, lacrimation, excessive sweating (diaphoresis), miosis, tachycardia, hypertension, tightness of the chest (bronchoconstriction).

## Both nicotinic and muscarinic receptors,

diarrhea, urinary incontinence, bradycardia, muscle twitching, fatigue, hyperglycemia, bronchospasm, and bronchorrhea.

## Nicotinic receptor

muscle weakness and flaccid paralysis.



# Cholinergic Toxidrome

| Muscarinic Symptoms | Nicotinic Symptoms |
| --- | --- |
| **S** – Salivation | **M** – Muscle cramps |
| **L** – Lacrimation | **T** – Tachycardia |
| **U** – Urination | **W** – Weakness |
| **D** – Defecation | **T** – Twitching |
| **G** – GI cramping | **F** - Fasciculations |
| **E** – Emesis | |

# Organophosphorus compounds (OP)

- **Acute Toxicity**

CNS cholinergic stimulation suppresses central medullary centers,

Depressed respirations, headache, anxiety, restlessness, confusion, psychosis, seizures, and coma

Death is secondary to respiratory paralysis and cardiovascular collapse.

# Organophosphorus compounds (OP)

- **Acute Toxicity** **Intermediate syndrome (IMS)**

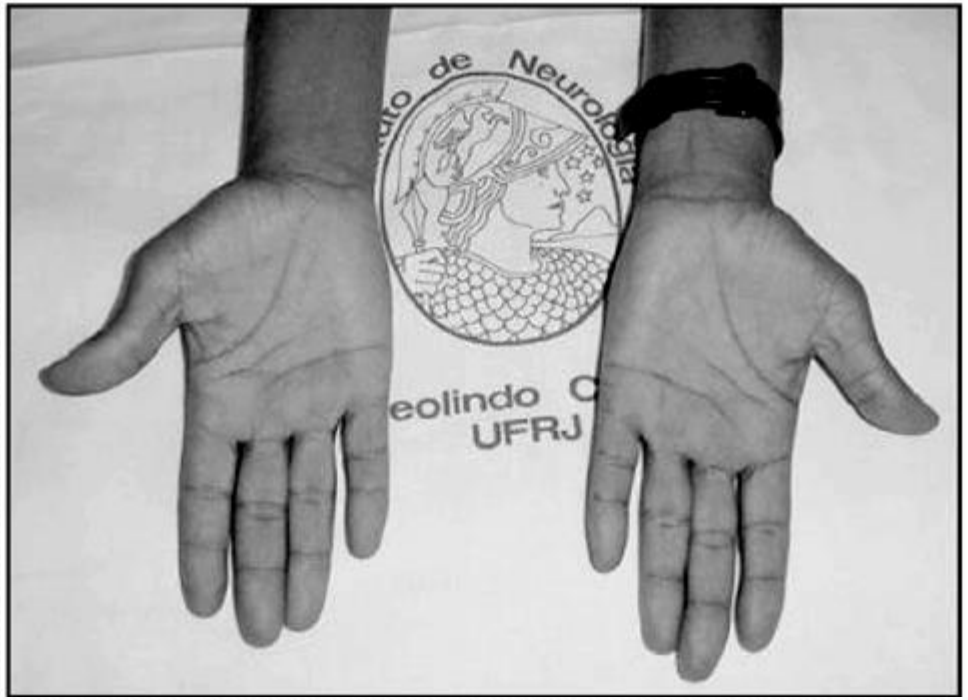
  - muscular paralysis innervated by **cranial nerves**
  - 24 h to 96 h after excessive exposure to Ops
  - 10-40% of patients
  - Patient cannot raise the head from the pillow
  - prolonged ACh-S inhibition at the neuromuscular junction.
  - No sensory impairment

# Organophosphorus compounds (OP)

- **Acute Toxicity**

## OP-induced delayed neuropathy (OPIDN)

- One to three weeks after exposure
- muscular weakness and paralysis of extremities, especially of hand and foot muscles, progressing to a persistent spastic spinal paresis
- inhibition of the neuronal enzyme, neurotoxic esterase, and ACh-S “aging.”



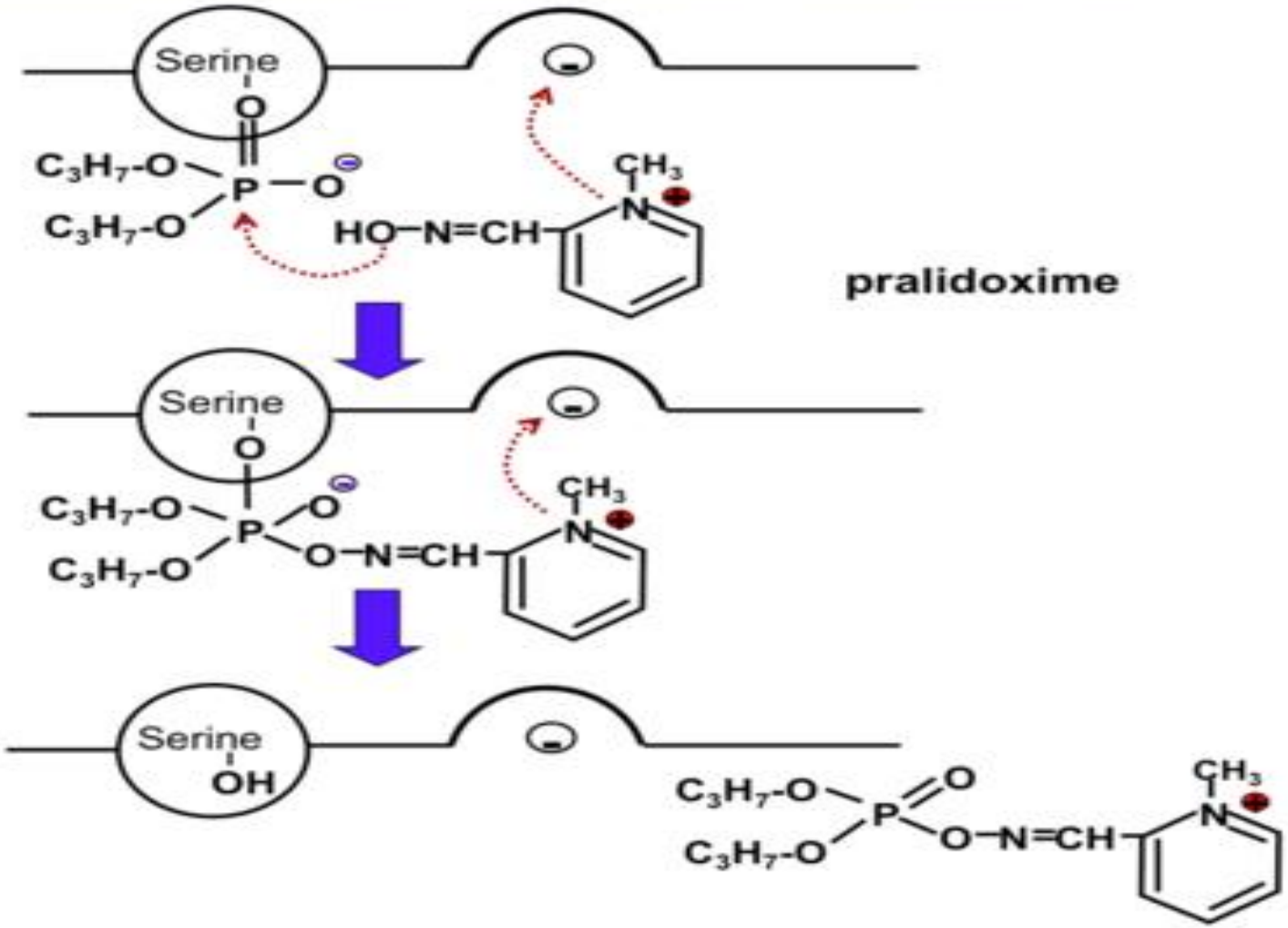
# Management of Acute poisoning of OPs

- Decontamination, airway stabilization, and activated charcoal

**Antidotes**

| Atropine | Oximes |
|---|---|
| | pralidoxime mesylate (P2S), pralidoxime chloride, and obidoxime |
| competitive antimuscarinic cholinergic antagonist | Reactivate ACh-S before enzyme Aging |
| central and peripheral autonomic receptors | severing the OP—ACh-S covalent bond at nicotinic, muscarinic, and central cholinergic sites<br>scavenge remaining OP molecules |
| I.V administration | I.V administration |

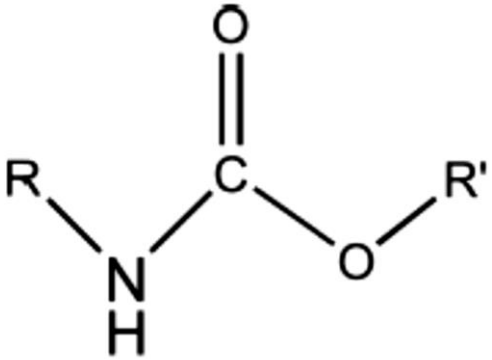
# Acetylcholinesterase Reactivator Mechanism



# Insecticides

## Carbamates

- **Aldicarb :** highly toxic
- **Carbofuran, Bufencarb, Methiocarb, Carbaryl**
- household and agricultural insecticides.
- Oral, dermal and inhalation



# Insecticides : Carbamates

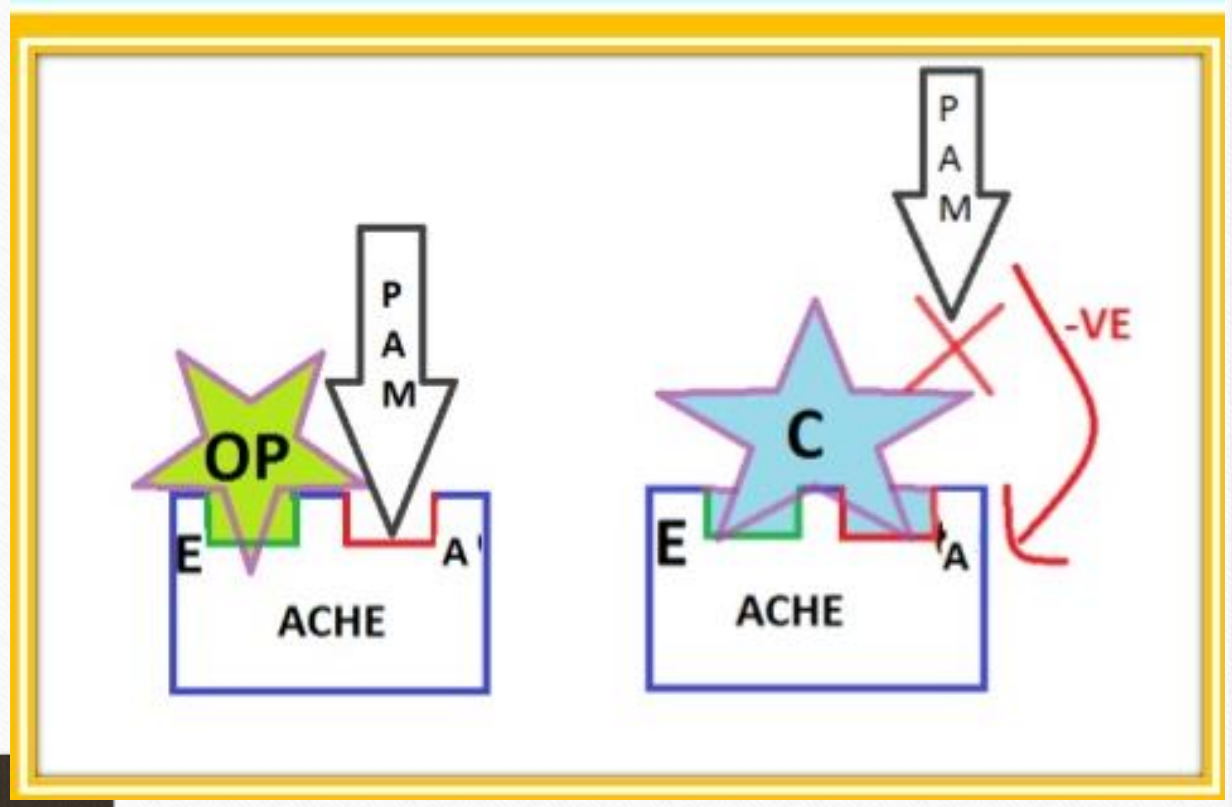
## Mechanism of Toxicity

- **Reversible** inhibition of acetylcholinesterase
- Carbamate–enzyme complex diassociates between minutes to hours
- Toxicity : shorter duration & less intensity
- Carbamates poorly penetrate BBB → less CNS toxicity

# Insecticides : Carbamates

## Management

- Only Atropine
- Pralidoxime increases toxicity
- No (Aging) of the enzyme



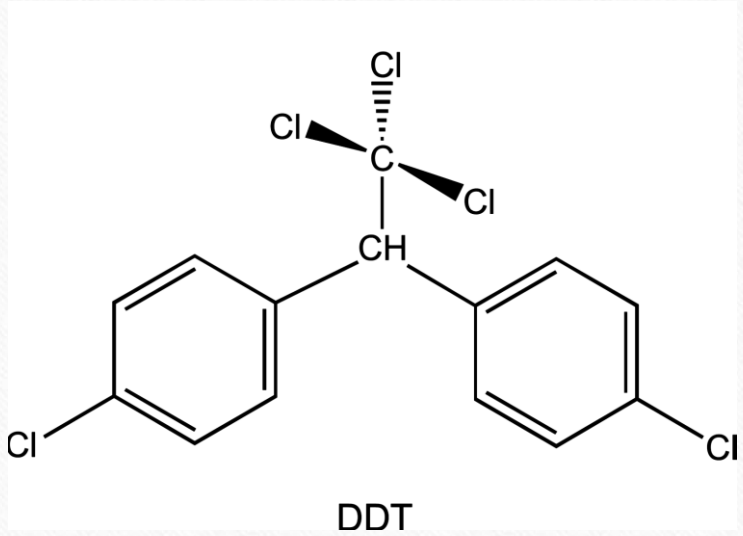
# Insecticides

## Organochlorine compounds (OC)

- Dichlorodiphenyltrichloroethane **(DDT)**
- Chlorinated cyclodienes: **Endrin, Dieldrin , endosulfan , chlordane**
- Benzene Hexachloride: **Lindane**

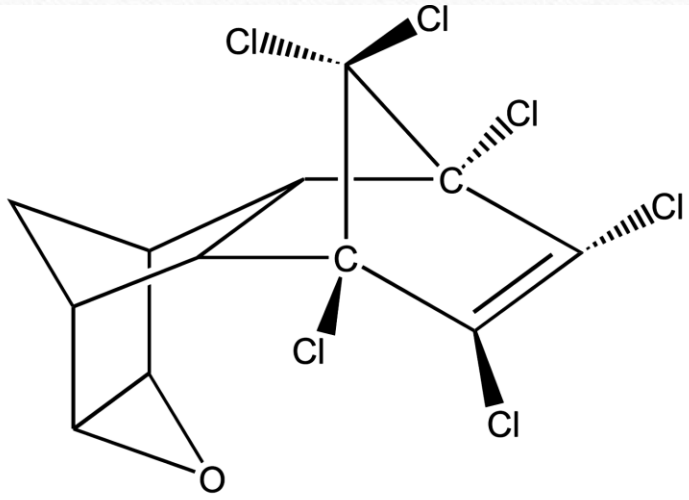
# Insecticides

## Organochlorine compounds (OC)

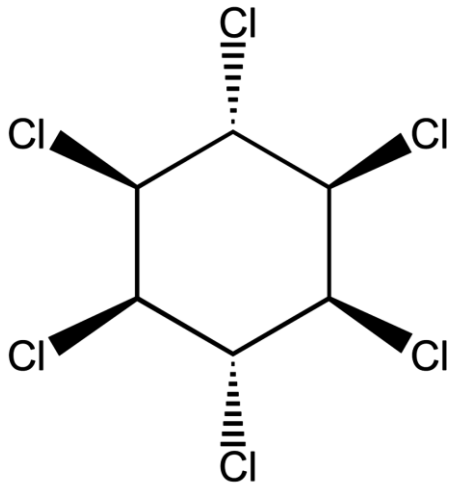



DDT

Dichlorodiphenyltrichloroethane (DDT)




Endrin




Lindane

# Insecticides

## Organochlorine compounds (OC)

**DDT** was developed during world war II

**Only used in areas where mosquito-borne malaria is a major public health problem**

**Cyclodienes** (Endrin, aldrin, dieldrin, endosulfan) have high lipid solubility, high carcinogenic potency

**No longer used**

**Lindane** is used in shampoo and lotion At 1% as pediculocide, scabicide, and ectoparasiticide

**itch mite (Sarcoptes scabiei), lice (Pediculus humanus sp.), and tick (dog and deer tick) infestations in humans**

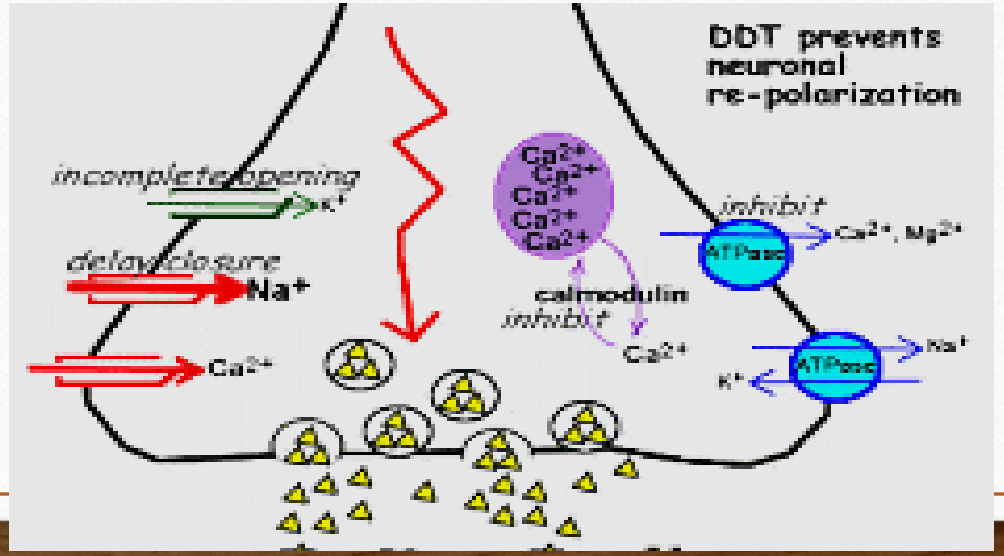
# Organochlorine compounds (OC)

## Mechanism of Toxicity

Chlorinated hydrocarbons are neurotoxins that interfere with transmission of nerve impulses, especially in the brain, resulting in behavioral changes, involuntary muscle activity, and depression of the respiratory center

- **DDT** delays closing of sodium channels

  ⇒ Prevent neuronal re-polarization

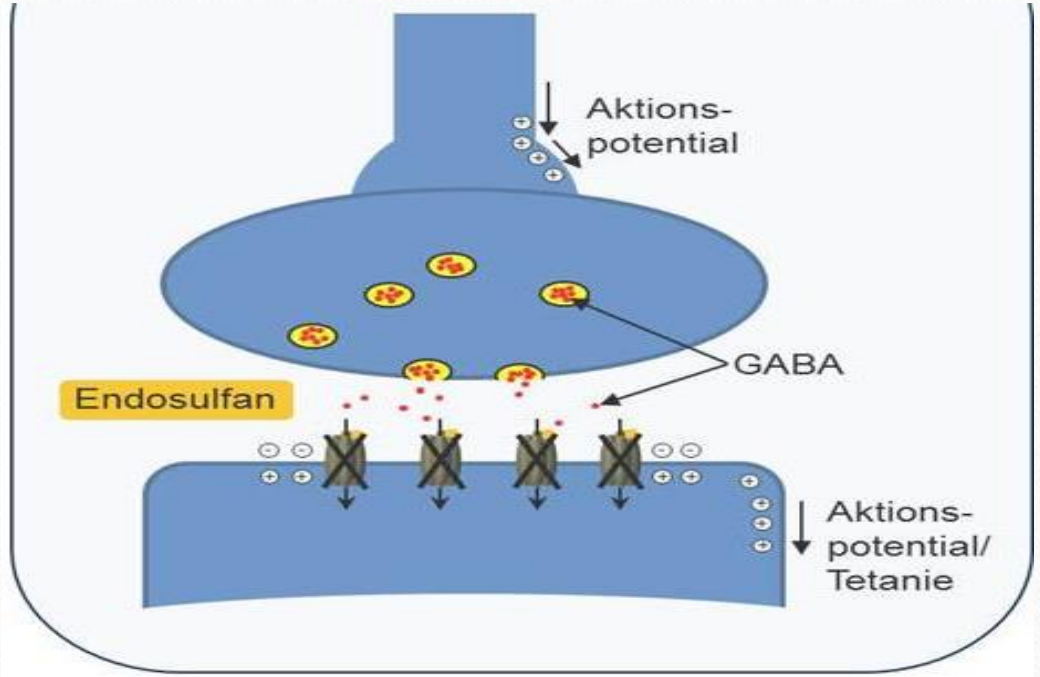


# Organochlorine compounds (OC)

## Mechanism of Toxicity

- **Cyclodienes and Lindane** block the chloride ion channel at GABA A receptor

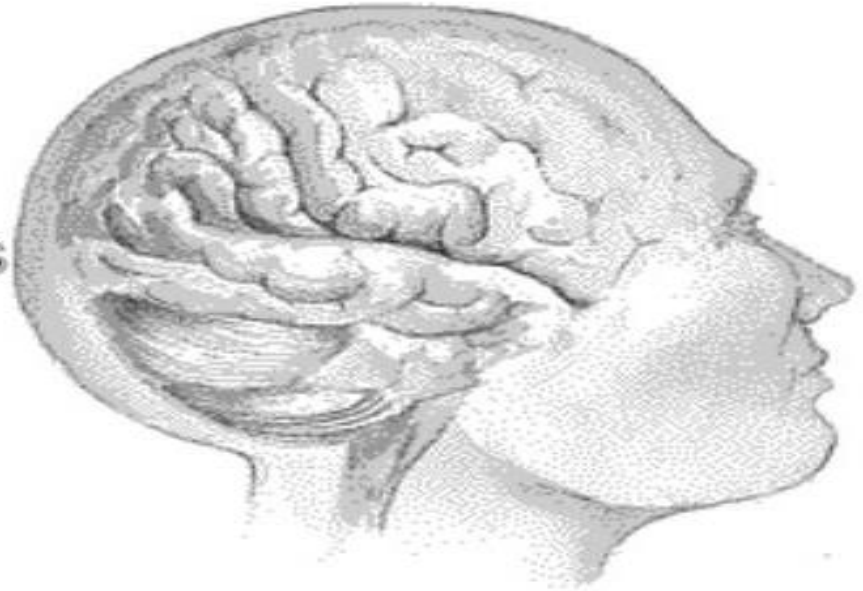
→ Inhibit GABA



# Signs and Symptoms of Acute Organochlorine [OC] Poisoning

- Muscle Weakness
- Dizziness
- Headache
- Numbness
- Nausea
- Loss of consciousness
- Convulsions
- Vomiting
- Hand tremors
- Staggering gait
- Anxiety/restlessness
- Confusion

Central Nervous System



**Arrhythmias**
**Liver /kidney injury**

e.g. *endosulfan* (Thiodan) and DDT

# Organochlorine compounds (OC)

## Clinical management

- Decontamination, gastric lavage, and administration of activated charcoal
- Myocardial arrhythmias are managed with antiarrhythmics such as lidocaine
- Benzodiazepines are indicated for preventing or reducing development of seizures

# Insecticides Pyrethroid Esters

- Derived from the naturally occurring compound **pyrethrum**
- **Pyrethrum** is obtained from dried flower heads of the yellow flower *Chrysanthemum cinerariaefolium*

| | |
|---|---|
| **pyrethrins type I** | allethrine, permethrin, and cismethrin |
| **pyrethrins type II** | fenvalerate, deltamethrin, and cypermethrin |

# Pyrethroid Esters

- Quick "knockdown" effect of flying insects, particularly flies and mosquitoes
- Pyrethrins are not well absorbed across the skin or from the GI tract
- Available in lotions, sprays, and shampoos for skin or scalp applications, as well as for removal from furniture and bedding material.

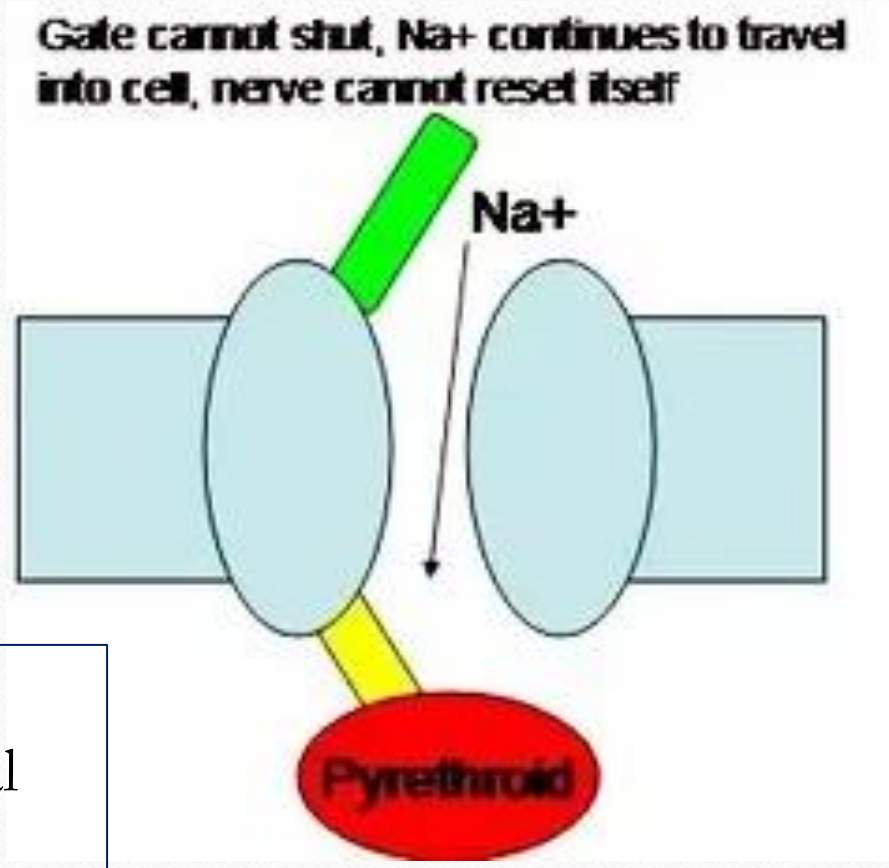

# Pyrethroid Esters

- Type I pyrethrins produce repetitive depolarization of axons by inhibiting inactivation of sodium channels.

- Type II pyrethrins have a similar mechanism but longer duration of action and also affect GABA receptor–mediated chloride channels.

- Toxicity to humans is associated primarily with hypersensitivity reactions. Treat with Oral or topical corticosteroids and H1-antihistamine blockers

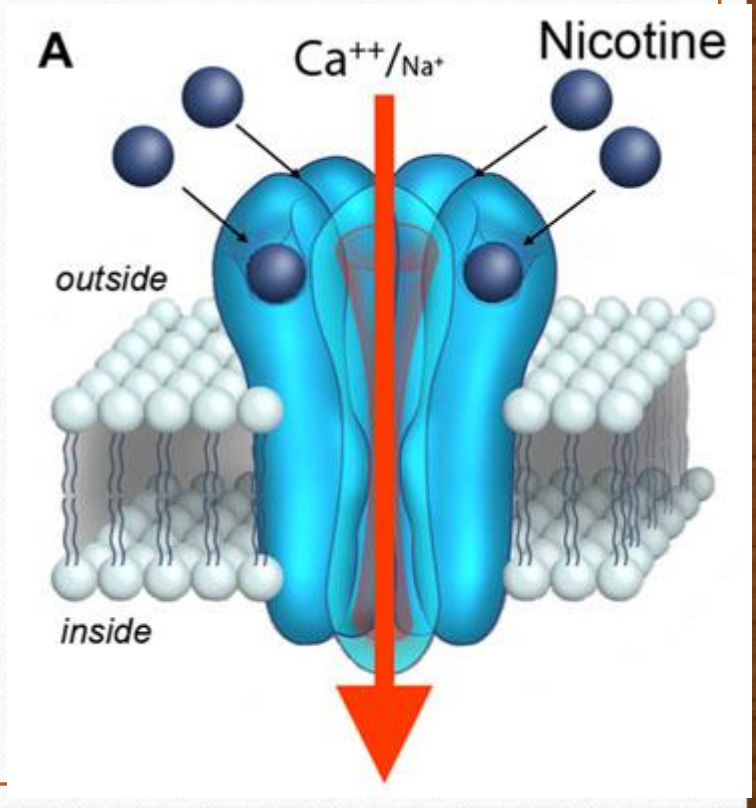
# Mechanism of Toxicity



# Insecticides
## Nicotine

- From the tobacco plant, *Nicotiana sp*

- Nicotine stimulates nicotinic receptors of all sympathetic and parasympathetic ganglia, the neuromuscular junction innervating skeletal muscle, and CNS pathways
- Nicotine affects the cardiovascular system, producing characteristic bradycardia or tachycardia

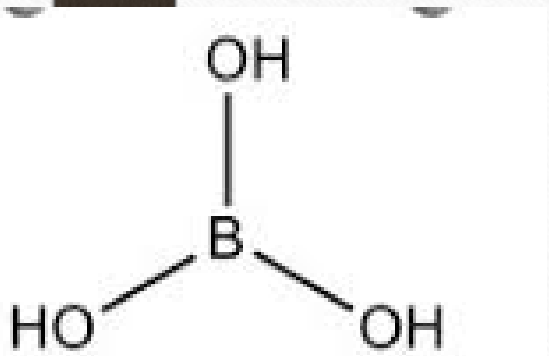



- Salivation, lacrimation, urination, defecation, vomiting.
- Muscular weakness, tremors, hypotension, and dyspnea.
- Convulsions and respiratory paralysis

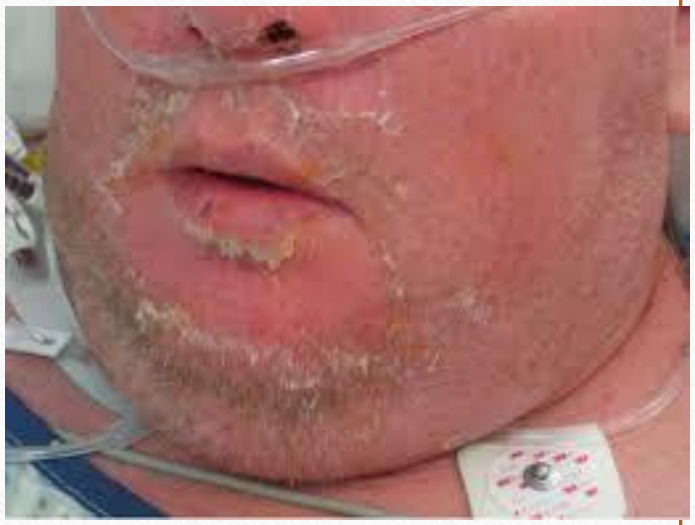
**Treatment**

**Mecamylamine** is a specific antagonist of nicotine actions

# Insecticides
## Boric acid

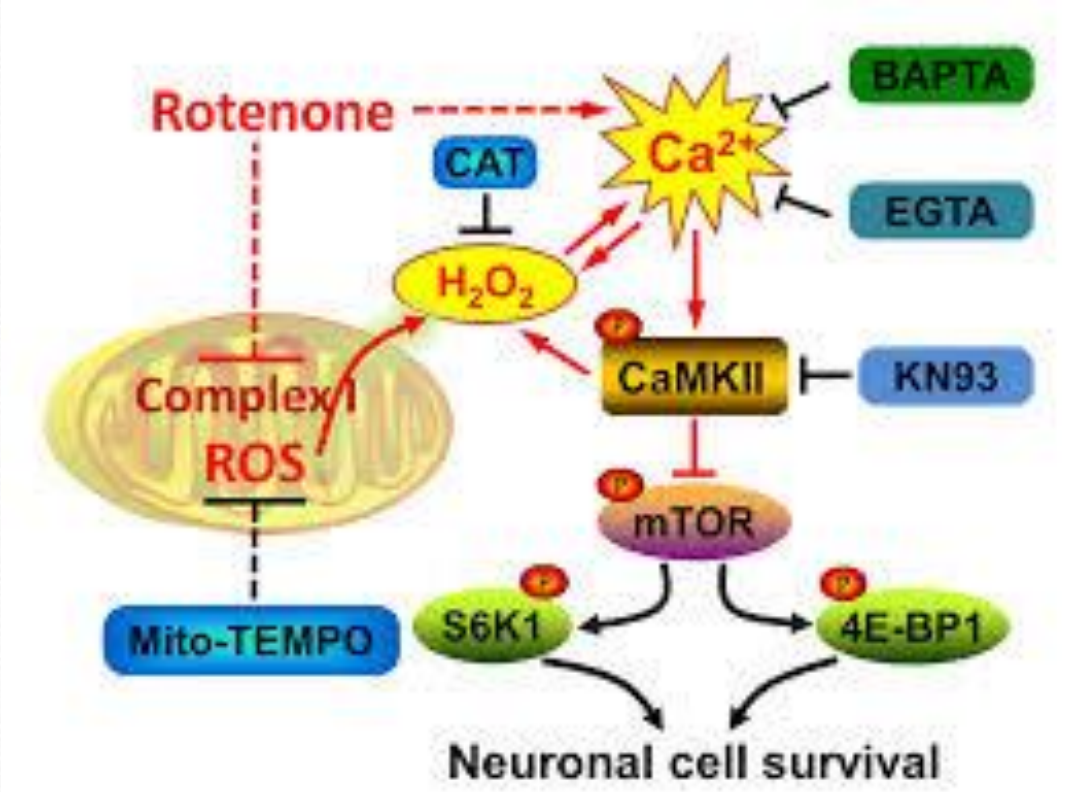



- Ant and roach killer.
- Undiluted powder + water + sugar or flour
- Erythrodermic rash ("boiled-lobster" appearance
- lethargy, fever, and muscular weakness, with progression to development of tremors and convulsions
- Decontamination, gastric lavage, hemodialysis and maintenance of vital signs



# Insecticides
## Rotenone

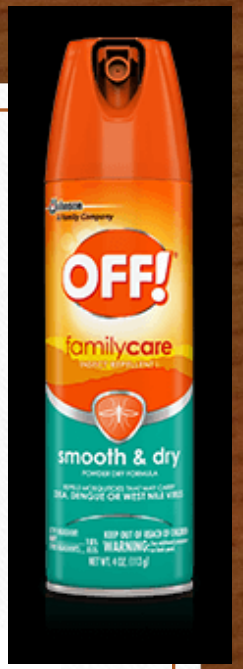
- Tubotoxin, derrin
- Derived from the Derris plant genus
- Quick knockdown of flying insects.
- Low toxicity
- Irritant, respiratory depression, seizures, and coma

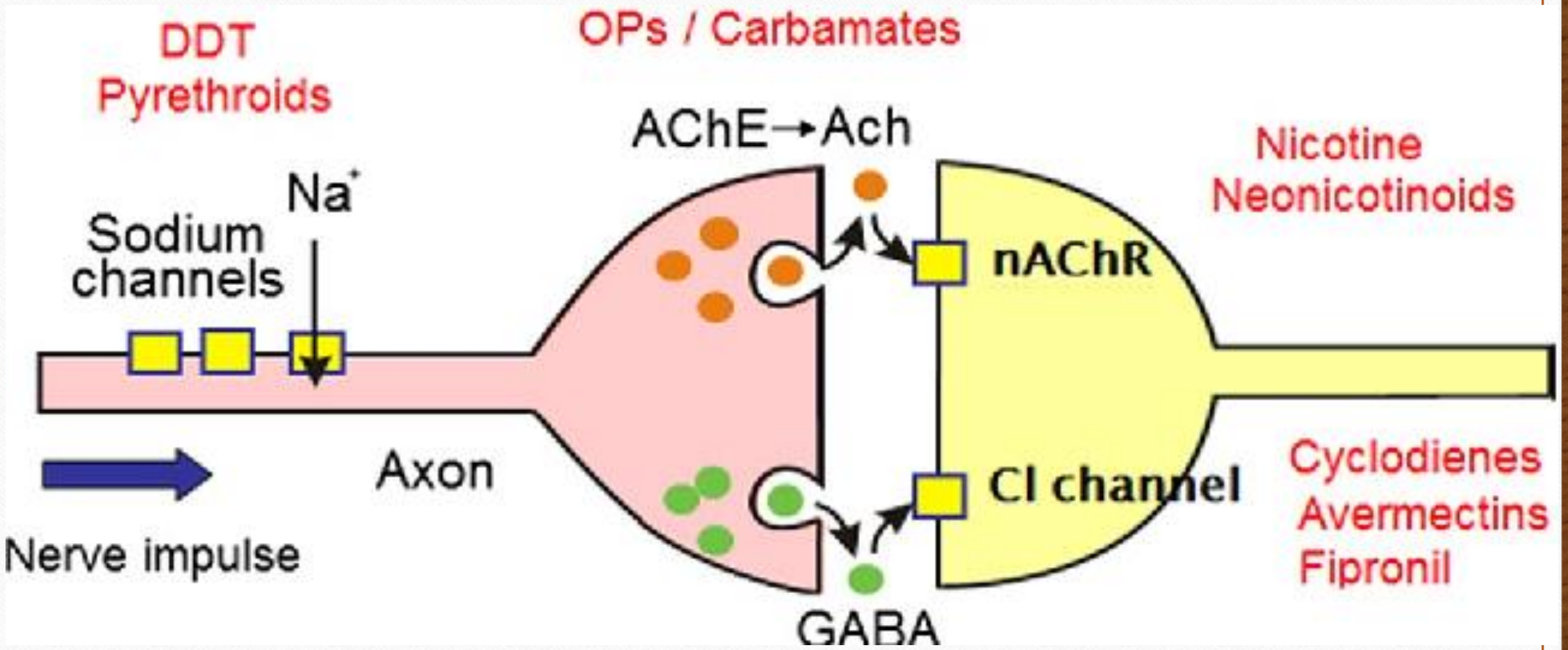



Depresses cellular respiration and inhibits mitotic spindle formation.

# Insecticides Diethyltoluamide (DEET)

- **Insect repellent** :Topical preparations at 5% to 100% concentrations
- applied directly to people's skin as a means to elicit a repelling action to keep insects from targeting human skin
- Stored in lipid compartments, resulting in a prolonged plasma half-life (2.5 hr)
- DEET blocks the olfactory receptors of insects for the volatile 1-octen-3-ol compound that is an element in human sweat and breath .
- Low toxicity : headache, lethargy, confusion, and tremors.





DDT
Pyrethroids
OPs / Carbamates
AChE→Ach
Nicotine
Neonicotinoids
Na+
Sodium
channels
nAChR
Cl channel
Cyclodienes
Avermectins
Fipronil
Axon
Nerve impulse
GABA

# Herbicides

- Chlorphenoxy compounds
- Triazines,
- Substituted ureas
- Dipyridyl herbicides
- mono- or dinitroaromatics.

# Herbicides

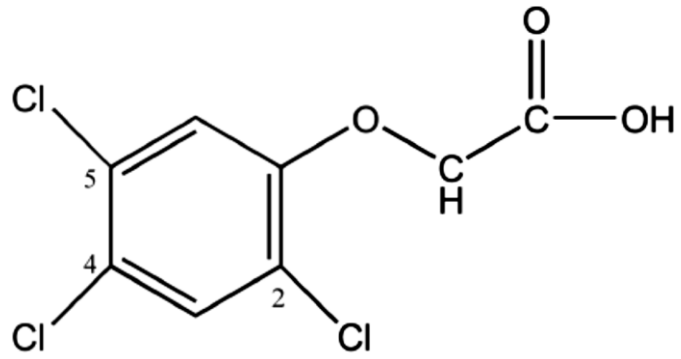
## Chlorophenoxy compounds

- **Selective herbicides**: eliminate undesirable plant species but produce little deleterious effects on other plants in the contact area.
- **Nonselective herbicides** destroy all plant life within the applied zone.

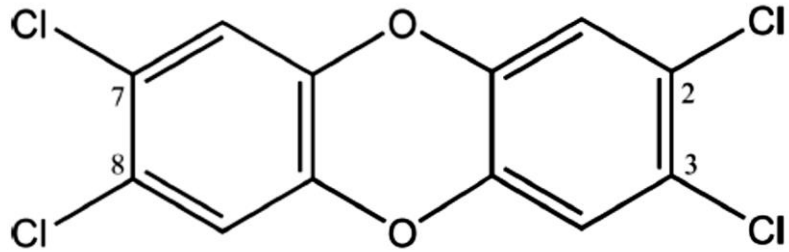
# Herbicides

## Chlorophenoxy compounds

- **TCDD (dioxin)** (2,3,7,8-Tetrachlorodibenzo- p-dioxin
- **2,4 –D** (2,4-dichlorophenoxy acetic acid)
- **2,4,5 T** (2,4,5- Trichlorophenoxy acetic acid)




2,4,5-T




dioxin

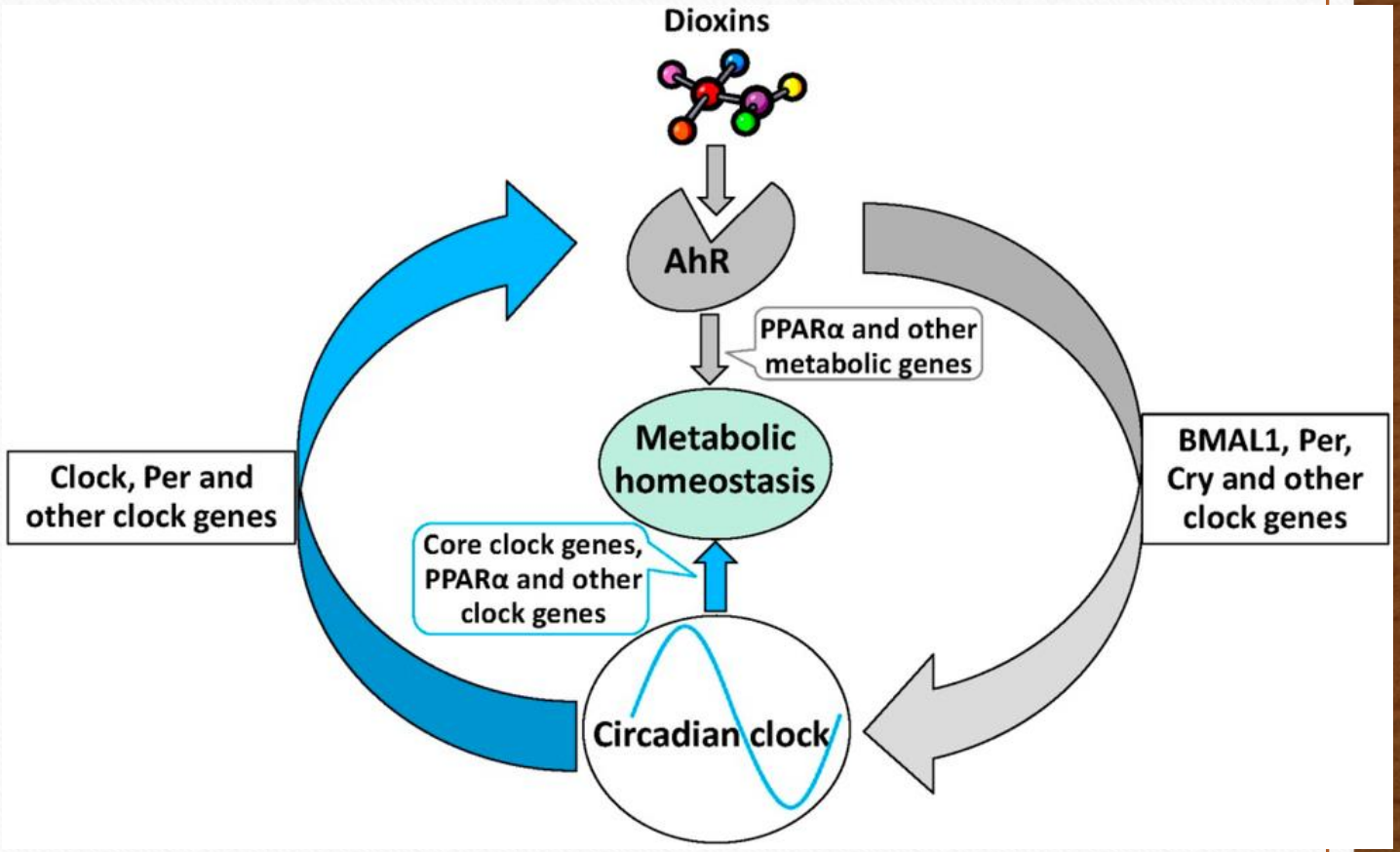
# Herbicides

## Chlorophenoxy compounds

- Agent Orange
- TCDD was used in Vietnam
- Cancer and birth defects


# Chlorophenoxy compounds Mechanism of Toxicity

- Dioxins are highly lipid-soluble
- Dioxins bind to the aryl hydrocarbon receptor protein (AhR) in cytoplasm
- hR activation by dioxins causes disruption of biochemical pathways involved in development and homeostasis
- Carcinogens



# Herbicides

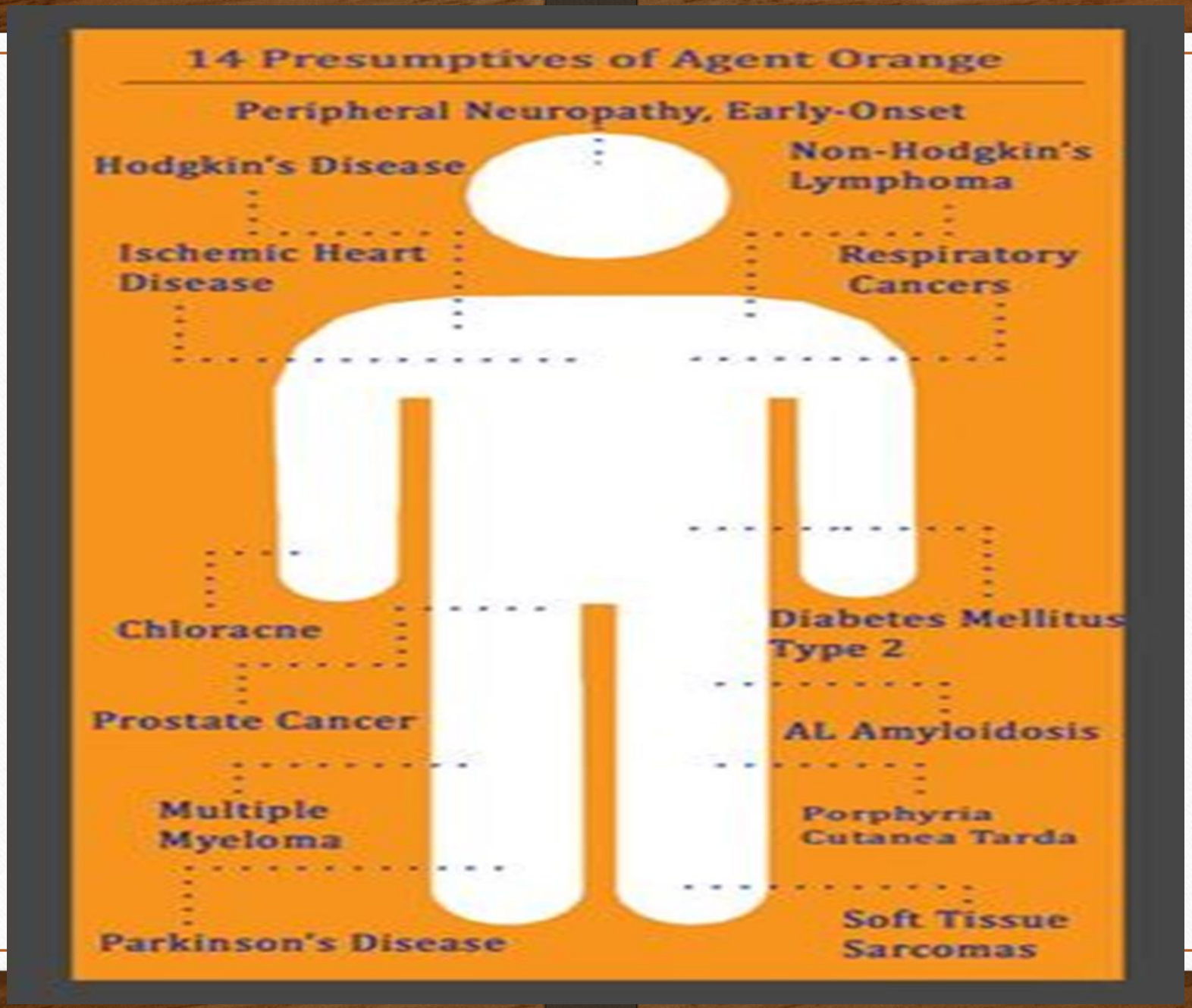
## Chlorophenoxy compounds

### Symptoms of Toxicity

- Irritation of the skin, eyes, and mucous membranes and nausea, vomiting,

↓ latency period
Several weeks

- **Chloracne**: a severe form of dermatitis
- Hyperpigmentation
- Neuropathy: sensory impairment and lower extremity motor weakness


14 Presumptives of Agent Orange
Peripheral Neuropathy, Early-Onset
Hodgkin's Disease
Non-Hodgkin's Lymphoma
Ischemic Heart Disease
Respiratory Cancers
Chloracne
Diabetes Mellitus Type 2
Prostate Cancer
AL Amyloidosis
Multiple Myeloma
Porphyria Cutanea Tarda
Soft Tissue Sarcomas
Parkinson's Disease

# Herbicides

## Chlorophenoxy compounds

### Clinical management

- Decontamination and washing exposed skin areas with mild soap neutralizes the acidic properties.
- Eye rinsing is important in case of ocular exposure
- alkaline diuresis may enhance renal elimination
- Administration of **olestra**, a nonabsorbable fat substitute that increases fecal excretion of dioxin.

**Olestra Is Only FDA-approved Noncaloric Fat Substitute**

# Herbicides

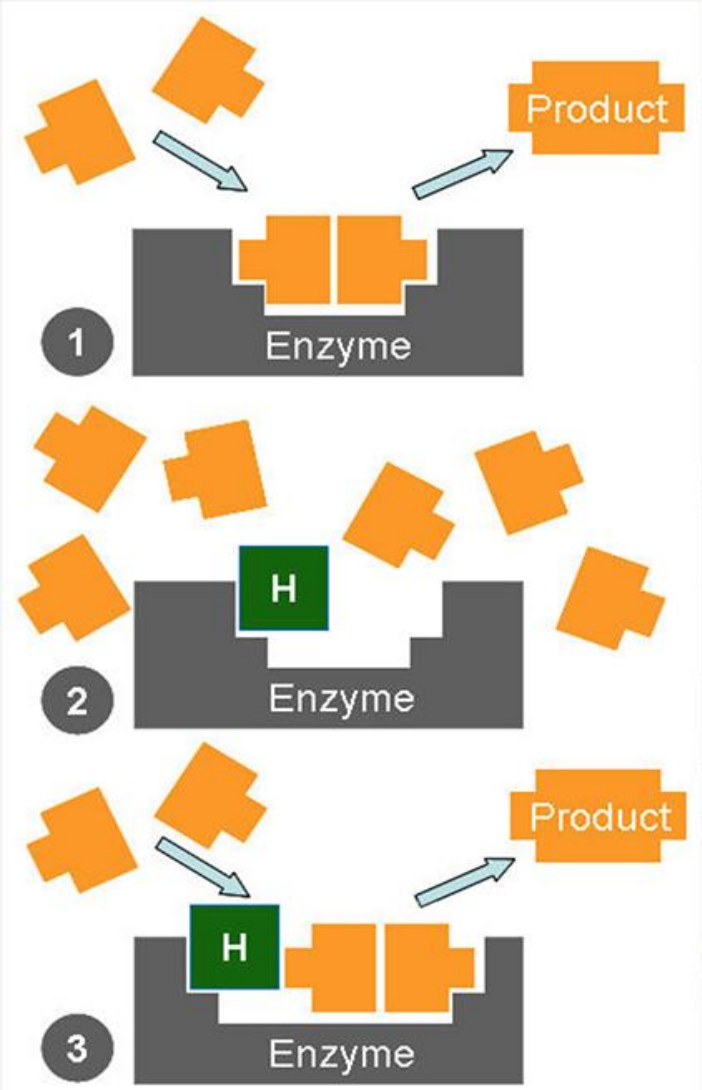
## Bipyridyl herbicides

- **Paraquat (PQ) and diquat** (PQ is more toxic)

The chemicals inhibit plant photosynthesis by interfering with nicotinamide adenine dinucleotide phosphate (NADPH/NADP) redox cycling

- **Contact herbicide**: promote reseeding of lawns and gardens within 24 hours after application

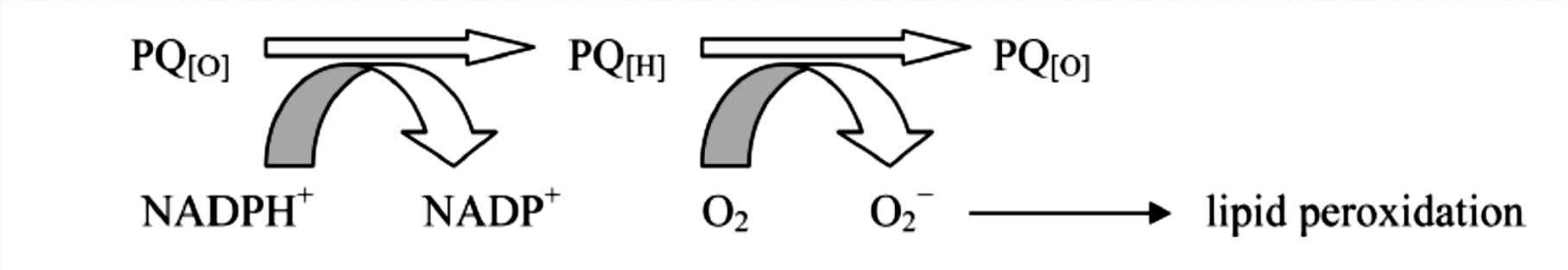
- PQ is poorly absorbed through skin and by inhalation



# Paraquat (PQ)

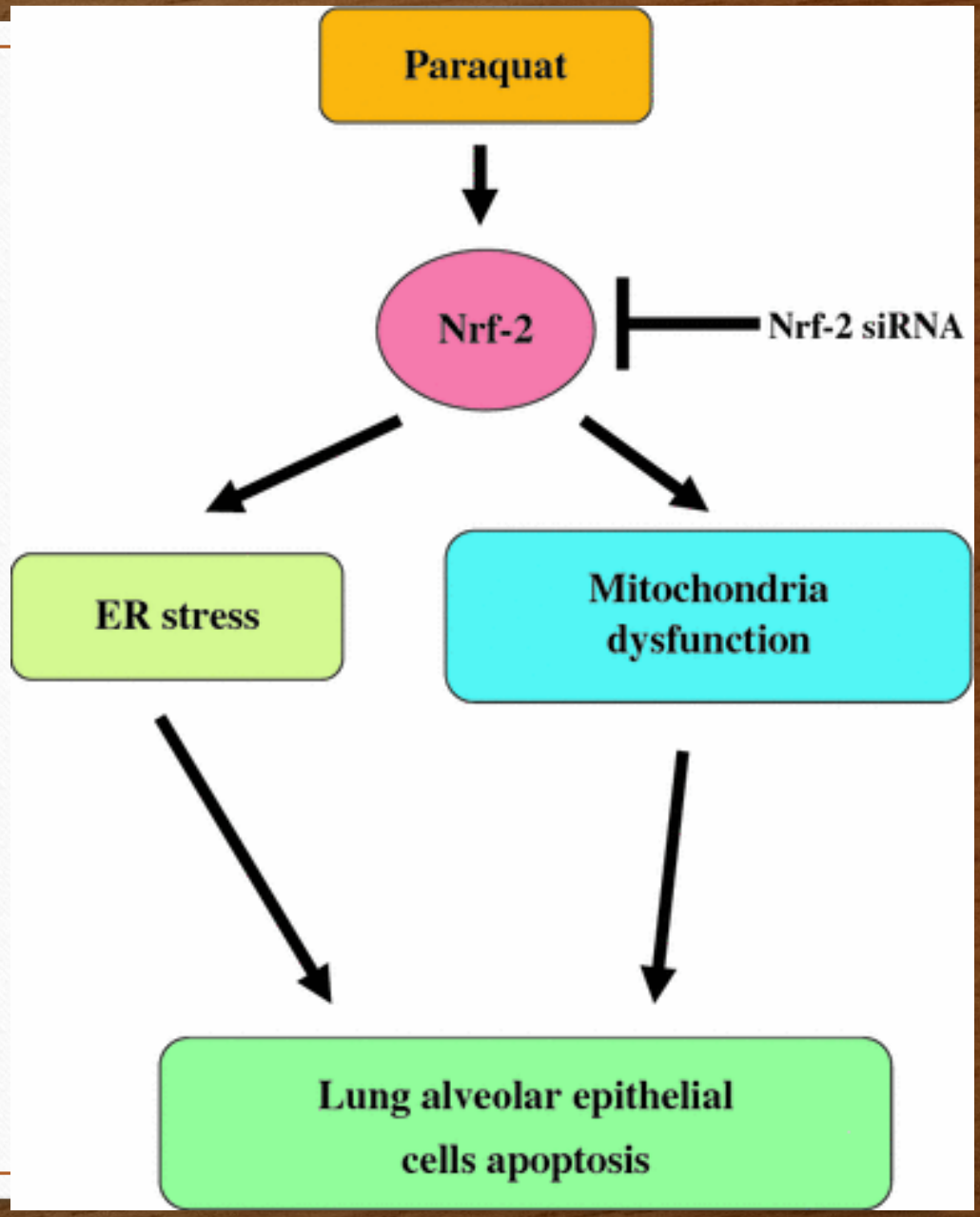
## Mechanism of Toxicity

- **Pulmonary Toxicity**




The oxidized (PQ[O]) compound accumulates in lungs and kidneys and undergoes redox cycling reactions (single electron reduction). It is metabolized by NADPH–cytochrome P-450–dependent reductase to the reduced (PQ[H]) intermediate radical. In turn, the reaction catalyzes the oxidation of NADPH to NADP, resulting in a depletion of the reducing equivalent

Glutathione (GSH) and superoxide dismutase also play a role as cellular defense factors against reactive oxygen species generated in tissues. GSH and superoxide dismutase depletion selectively enhances PQ-induced oxidative stress by further inhibiting the cell's ability to prevent against damaging effects of free-radical generation. In addition, dismutated oxygen (O:, singlet O2) accumulates from O2, producing an excess of hydroperoxides. This precipitates a series of potentiating reactions undermining the stability of unsaturated lipids within cell membranes.



# Paraquat (PQ)

## Symptoms of Toxicity

- PQ selectively concentrates in alveolar type I and type II pneumocytes, and in renal epithelial cells

- **Hit and Run**: redox cycling and free-radical formation occur after the toxin is eliminated

**Diquat** is not taken up by pulmonary alveolar cells and does not cause pulmonary fibrosis, but it has been associated with CNS hemorrhagic infarctions.

**TABLE 29.2** Phases of PQ Toxicity and Associated Clinical Effects

| Phases of toxicity | Time range (days) | Minimum dose (mg/kg) | Toxic effects: Oral ingestion | Toxic effects: Local exposure |
|---|---|---|---|---|
| 1 I. Asymptomatic or mild | 1–5 | 20[a] | NVD, ulceration, intestinal hemorrhage, hemoptysis, oliguria | GI, dermal, and ocular irritation |
| 2 II. Moderate to severe | 2–8 | 20–40 | V, D, systemic accumulation, pulmonary fibrosis | Severe GI, dermal, and ocular irritation; inflammation; ulceration of skin and mucous membranes |
| 3 III. Severe: acute fulminant toxicity | 3–14 | >40 | Liver, kidney, cardiac, and pulmonary failure | Marked ulceration as with phase II |

[a]Doses as low as 4 mg/kg have resulted in death.

*Abbreviations*: GI, gastrointestinal; PQ, paraquat; NVD, nausea, vomiting, diarrhea.

# Paraquat (PQ)

## Clinical management

- Maintain an open airway and assist ventilation
- Avoid excessive oxygen administration, as oxygen is the substrate from which dipyridyls create harmful free radical species
- Treatment with cyclophosphamide and glucocorticoids has been effective for moderate-to-severe paraquat poisoning

# Other Herbicides

**The triazines (Atrazine) , substituted ureas (monuron), and nitroaromatic and chloroanilide classes (Dinoseb)**

- They are frequently used as contact, pre-emergence, and select herbicides.
- Their low to moderate toxicity to humans and animals make them suitable for agricultural, industrial, and household utility.

# Rodenticides

- **Anticoagulants:** warfarin and superwarfarin
- **Phosphorous**
- **Red Squill**
- **Metals : Thalium and Barium**

# Rodenticides

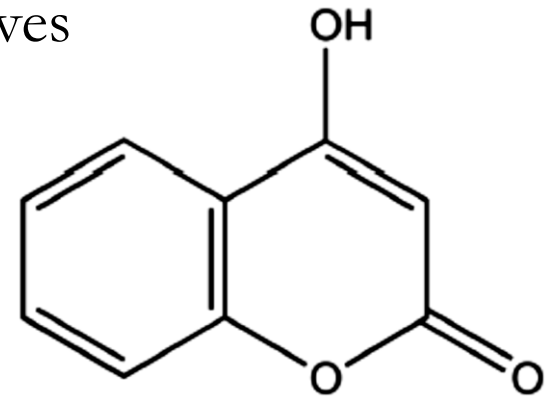
## Anticoagulants

- **Warfarins** (the carbon-3 substituted 4-hydroxycoumarin derivatives require a minimum of 21 days of several feedings

- **Superwarfarins** (brodifacoum, indandiones): combat rodent resistance

They are lethal after only one or two feedings

**Superwarfarins** are estimated to be 100 times as potent as warfarin




4-hydroxycoumarin

# Rodenticides

## Anticoagulants

- **Absorption**: Complete and rapid
- **Distribution** : Completely bound to plasma proteins (97-99%), localize in lipid and protein compartment
- **Elimination**: Very long half-life (35 hours)

**Sweet clover plant**

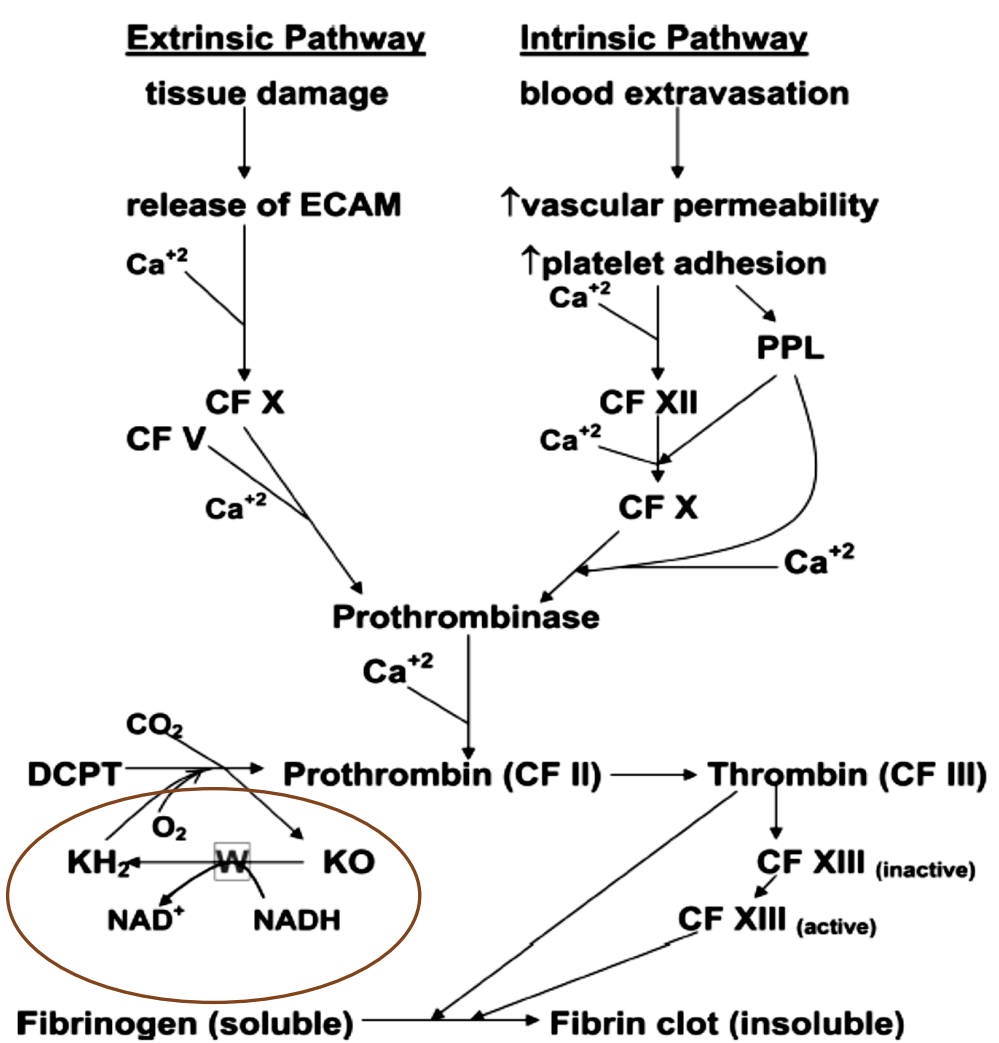
# Anticoagulants

## Mechanism of Toxicity

- Vitamin K antagonist

Warfarins inhibit the carboxylation of glutamate residues (Glu) to gcarboxyglutamate (Gla) in the conversion of descarboxyprothrombin (DCPT) to prothrombin (**clotting factor II**)

Only the synthesis of new factors is affected, and the anticoagulant effect is delayed until currently circulating factors have been degraded..



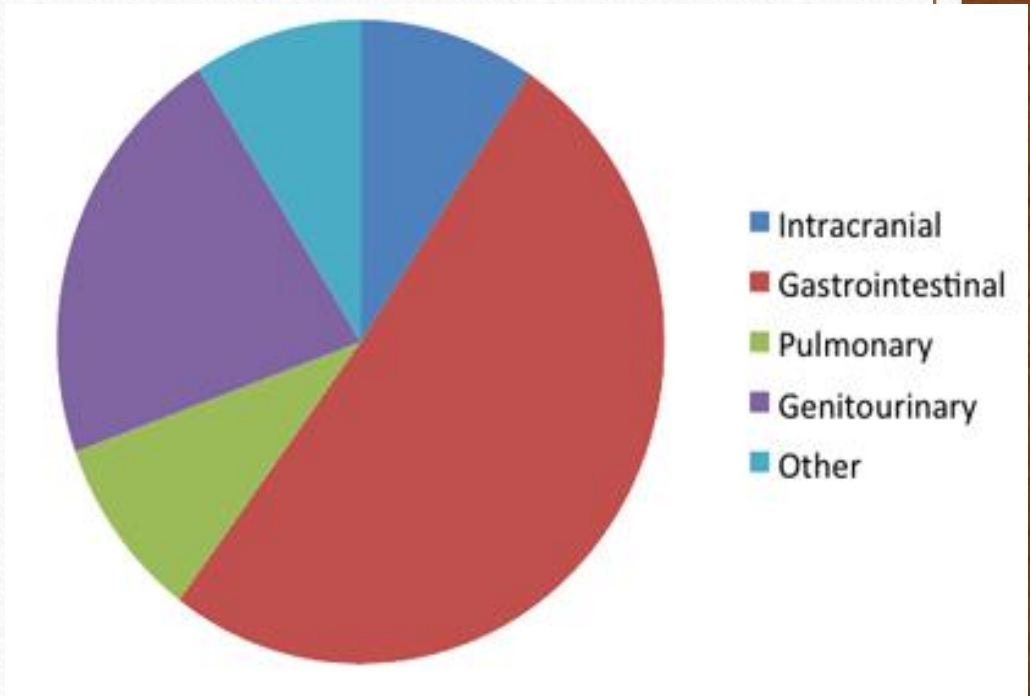
# Anticoagulants

## Symptoms of Toxicity

The earliest onset of toxicity or clinical activity is not obvious until at least 21 to 72 hours after exposure

- Gingival bleeding, epistaxis, joint and muscle pain, easy bruising, and an abnormal prothrombin time (PT).
- hematuria, bloody stools, intracranial hemorrhage, and shock.

**Warfarin bleeding**



# Anticoagulants

## Clinical management

- **Replacement of blood loss**: fresh frozen plasma (FFP)

**Antidote: Vitamin K1 (phytonadione):** IV administration of this active form of vitamin K rapidly corrects PT within 24 hours**.** Maintenance with the oral dosage form

Measure PT/INR,

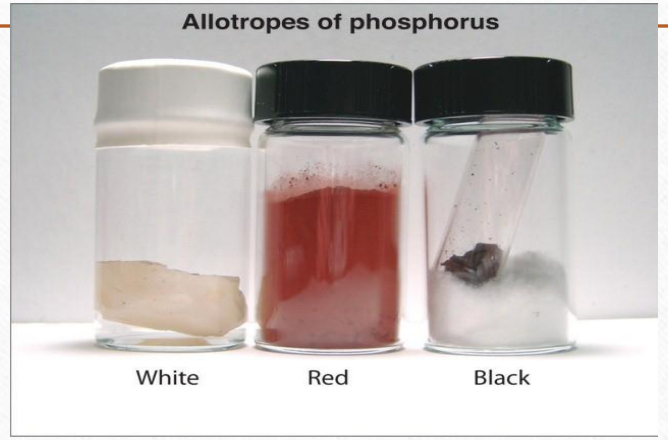
**Other vitamin K derivatives, K3 (menadione) and K4 (menadiol), are therapeutically ineffective.**

## TABLE II–65. WARFARIN INTERACTIONS (SELECTED EXAMPLES)

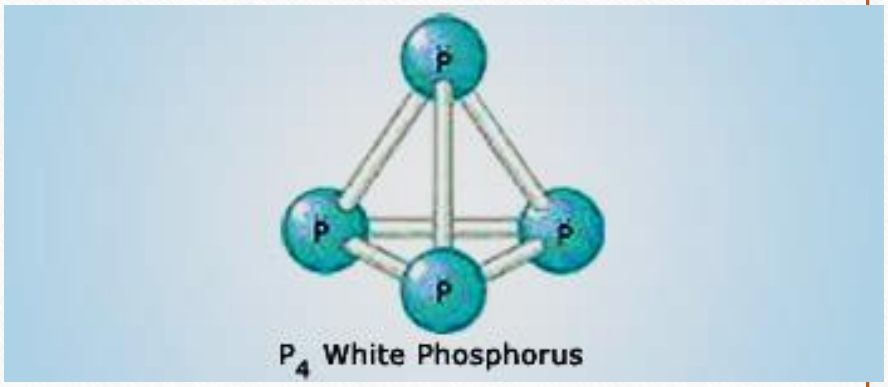
| Increased Anticoagulant Effect | Decreased Anticoagulant Effect |
|---|---|
| Acetaminophen | Antibiotics |
| Allopurinol | Azathioprine |
| Amiodarone | Barbiturates |
| Anabolic/androgenic steroids | Carbamazepine |
| Antibiotics/Antifungals | Cholestyramine |
| Anticoagulant/antiplatelet drugs | Glutethimide |
| Capecitabine | Green Tea |
| Chloral hydrate | Nafcillin |
| Cimetidine | Oral contraceptives |
| Disulfiram | Phenytoin |
| Ginkgo biloba | Rifampin |
| Mirtazapine | St. John's wort |
| Nonsteroidal anti-inflammatory agents | Vitamin K containing foods |
| Quinidine | |
| Salicylates | |
| Selective serotonin reuptake inhibitors | |
| Sulfonamides | |

# Rodenticides

## Phosphorous




- **White (elemental) phosphorus** is a white or colorless, spontaneously flammable, highly toxic solid.
  - ❖ Rodenticide
  - ❖ Oral ingestion, fume inhalation , burning
  - ❖ Cellular toxicity



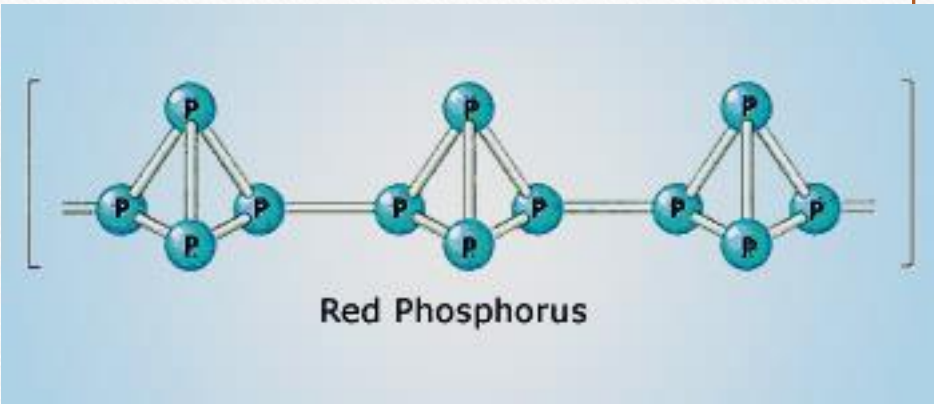

White phosphorus —**Air**→ Phosphorous pentoxide —**Water**→ Phosphoric acid

# Rodenticides

## Phosphorous

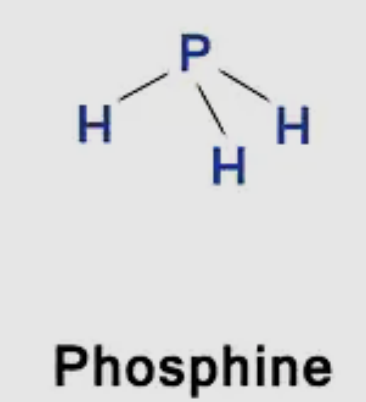
- **Red phosphorus** is less toxic and a less reactive but flammable compound
  - ❖ Safety matches and smoke bombs and fireworks

❖ reactant for the manufacturing of pyrotechnic substances, fertilizers, phosphorus halides, and rodenticides




**Phosphine** is a flammable, highly toxic colorless gas with a characteristic fish odor.

❖ used as a fumigant rodenticide and insecticide , in the production of electronic components.



# Phosphorous

## Mechanism of Toxicity

**Halides, oxides, and sulfides of phosphorus** : pulmonary irritants and dermal corrosive compounds.

They are capable of spontaneous ignition producing flames and fumes.

They can combine with moist air or oxidizing agents to generate irritating or corrosive acidic conditions.

**Phosphate esters** (organic phosphates such as triethyl phosphate) inhibit acetyl cholinesterase. Oral ingestion, therefore, produces neurotoxicity, muscular weakness, and paralysis

# Phosphorous

## Symptoms of Toxicity

- **white phosphorus** is associated with nausea, vomiting, diarrhea, phosphorescent vomitus, and stools (known as the **smoking stool syndrome**).

- Mucosal burning, abdominal pain, and a characteristic "garlic odor" to the breath are frequent complaints from gastrointestinal irritation.

- Tremors, convulsions, jaundice, liver and cardiovascular failure, and coma develop following severe intoxication.

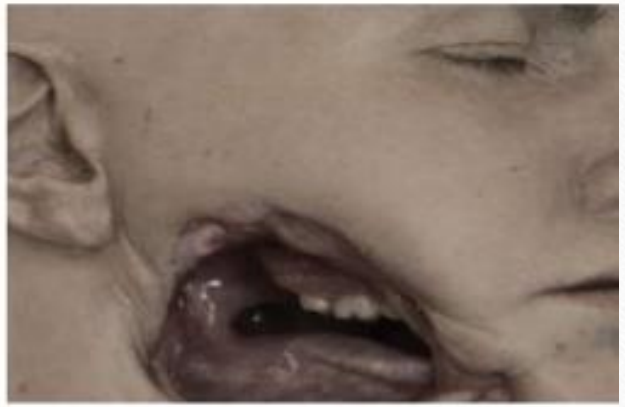
- Mortality rates of approximately 25% to 75% are noted from complications of systemic toxicity

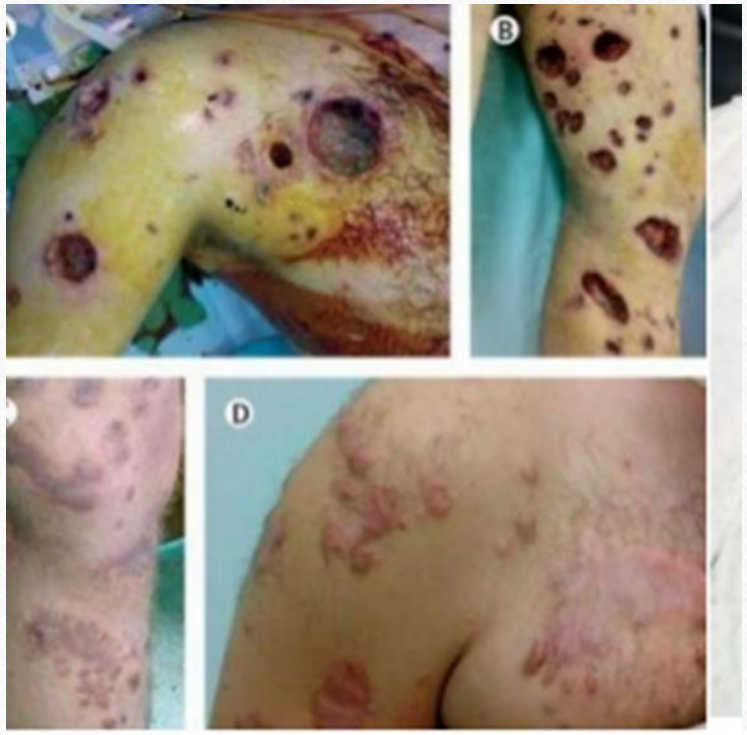
# Fume inhalation

- Long term inhalation leads to <u>osteonecrosis of jaw (Phossy Jaw)</u>

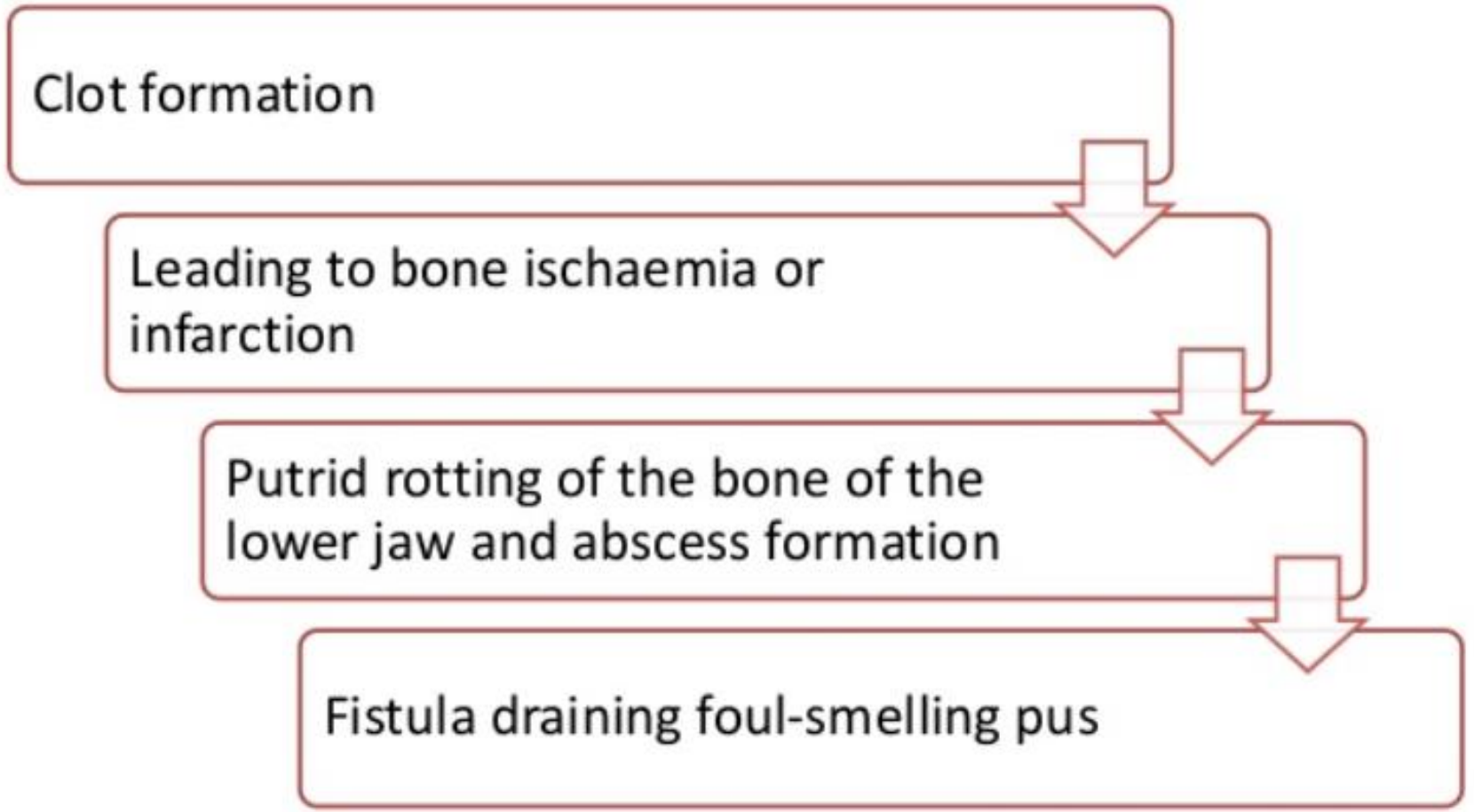
- Began with toothache and swelling of gums and jaw

Chronic, low-dose exposure to phosphates risks their accumulation in the skeleton.






Second or third degree burn


Clot formation
Leading to bone ischaemia or infarction
Putrid rotting of the bone of the lower jaw and abscess formation
Fistula draining foul-smelling pus

# Phosphorous

## Mechanism of Toxicity

**Phosphine gas :** solid rodenticides, such as zinc or aluminum phosphides, contact oxidizing agents or weak acids

- "fish odor" to the breath, especially when the powder mixes with stomach acid.

- Upper respiratory tract (URT) and lower respiratory tract (LRT) injury

URT: local inflammation and irritation of ocular, oral, and nasal mucous membranes, including conjunctivitis, lacrimation, rhinitis, and pharyngitis.
LRT : cough, wheezing, and tightness of chest with painful breathing.

nausea, fatigue, tremors, dizziness, and hypotension, followed by pulmonary edema, cardiogenic shock, central nervous system depression, convulsions, and coma.

# Phosphorous

## Clinical management

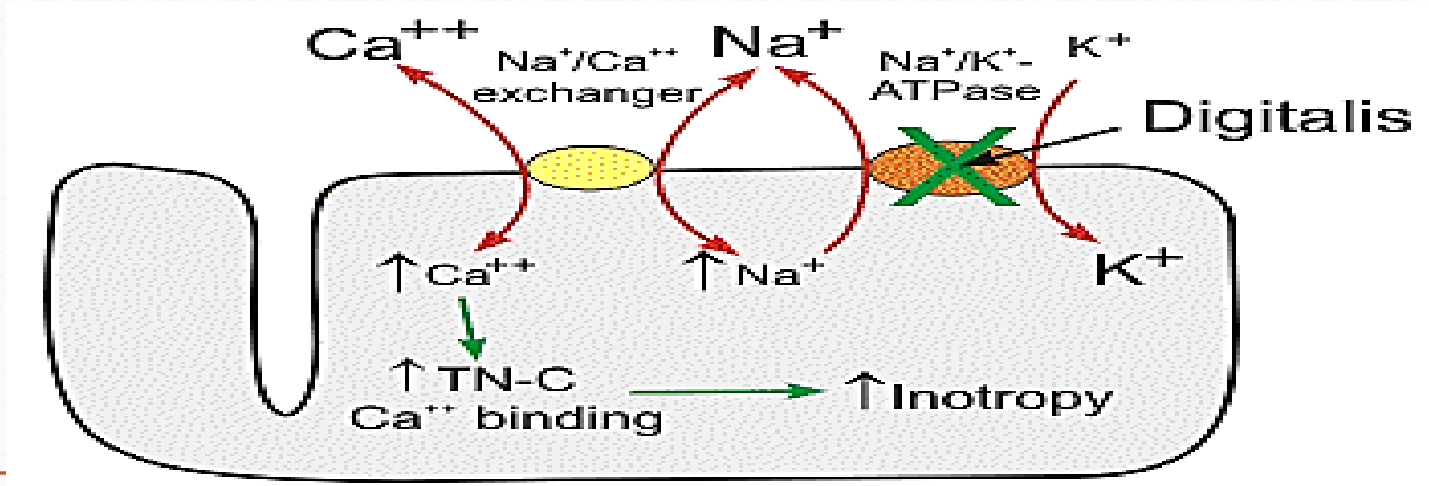
- Gastric lavage and administration of activated charcoal to reduce absorption
- Give sodium bicarbonate neutralize acidity
- Induction of vomiting is generally not recommended due to phosphorus's potentially corrosive nature

# Rodenticides

## Red squill

- Squill contains many digoxin-like cardioactive glycosides, of which scillaren A, scillaren B, and proscillaridin A

- Toxicity is similar to that of digoxin.
- Inhibit the function of the sodium-potassium-ATPase pump.

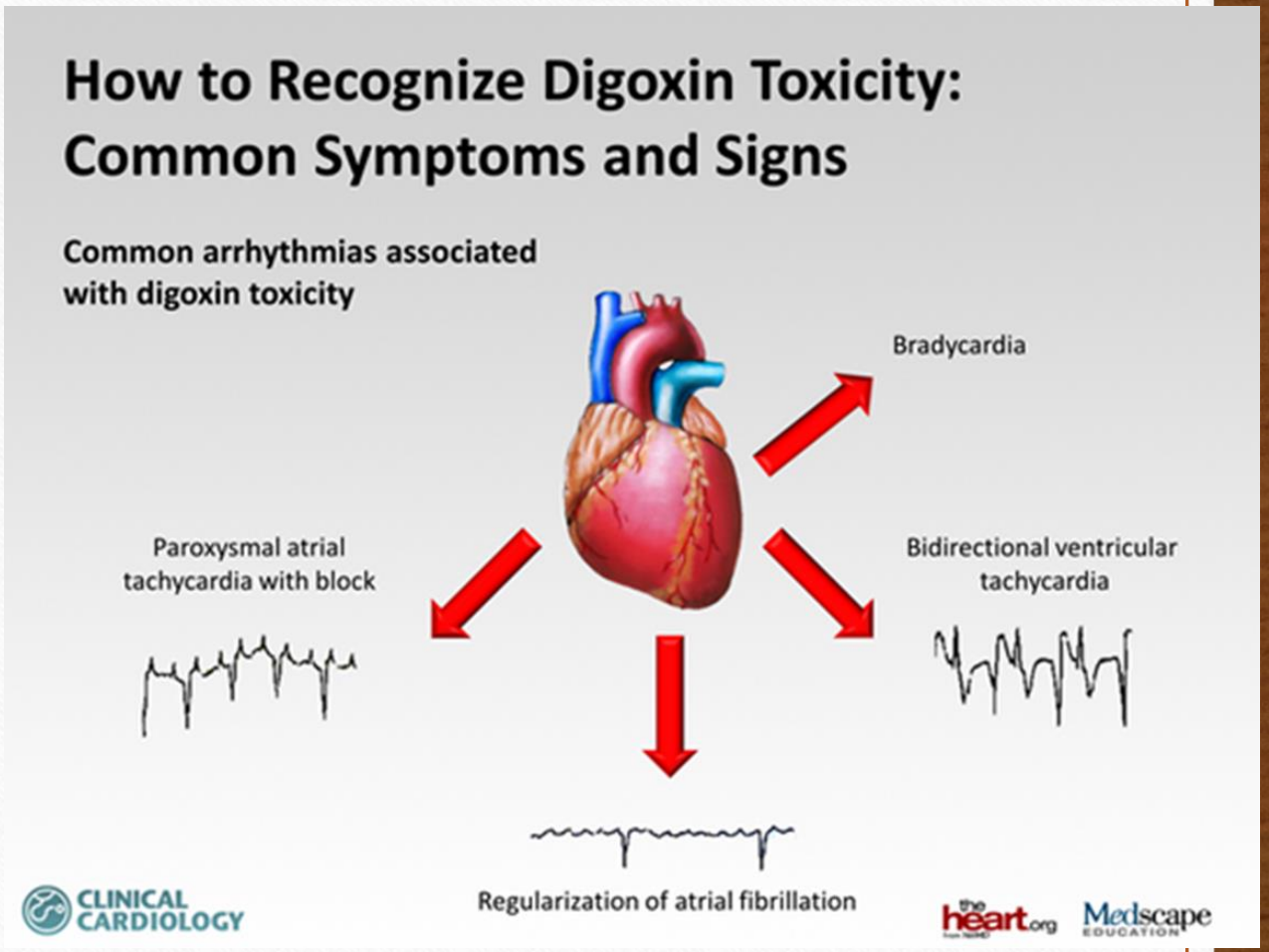


# Rodenticides

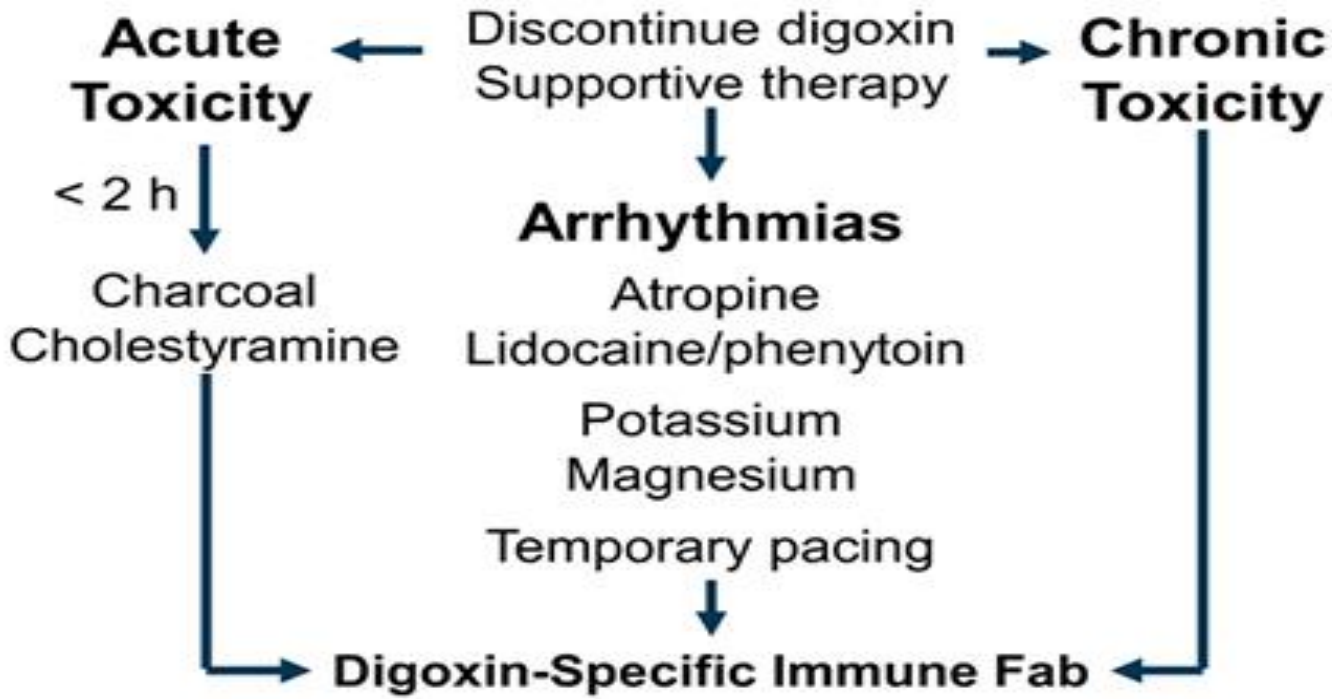
## Red squill

- Initial symptoms appear as blurred vision, arrhythmias, convulsions, and coma

- Rodents do not possess a vomiting reflex and consequently succumb to cardiac arrest, respiratory failure, and convulsions).

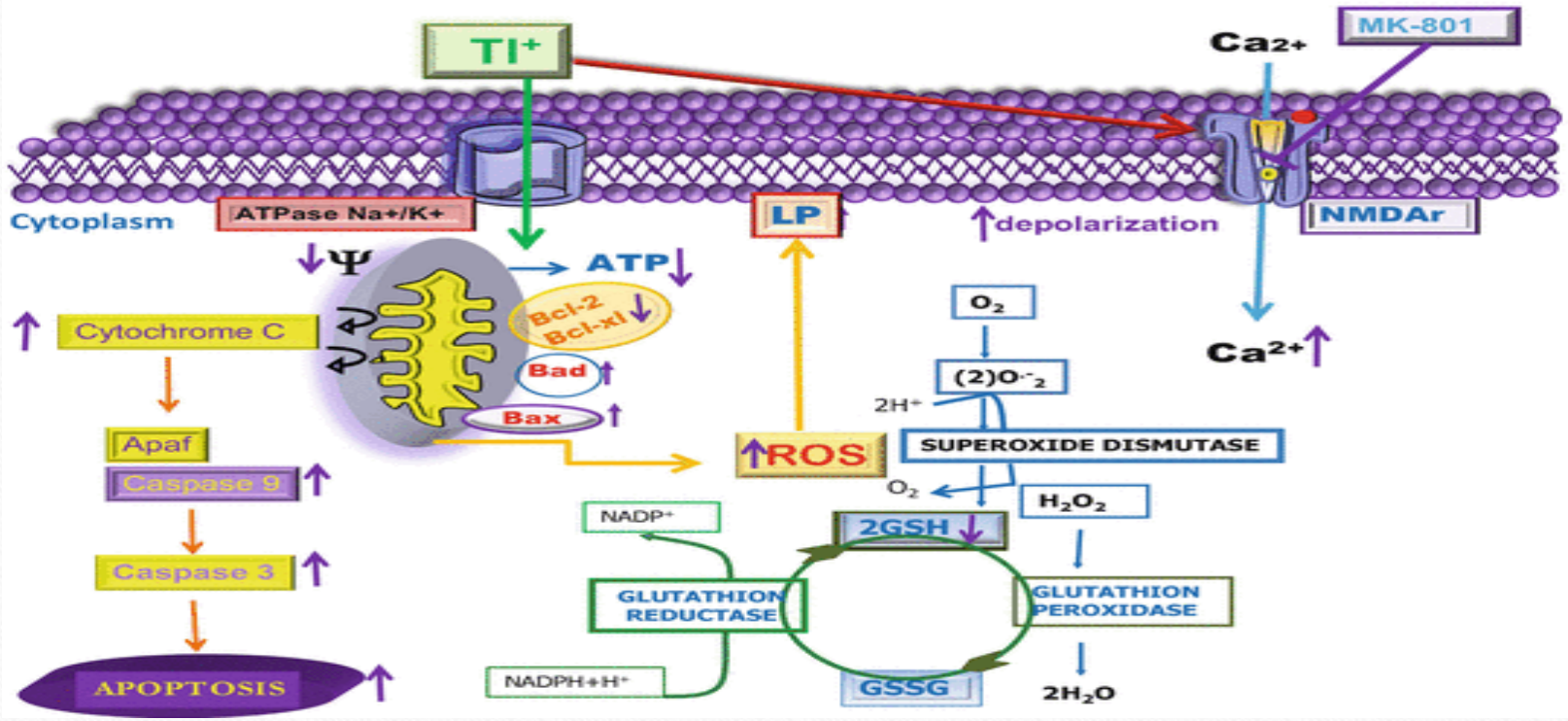


# Management of Digoxin Toxicity



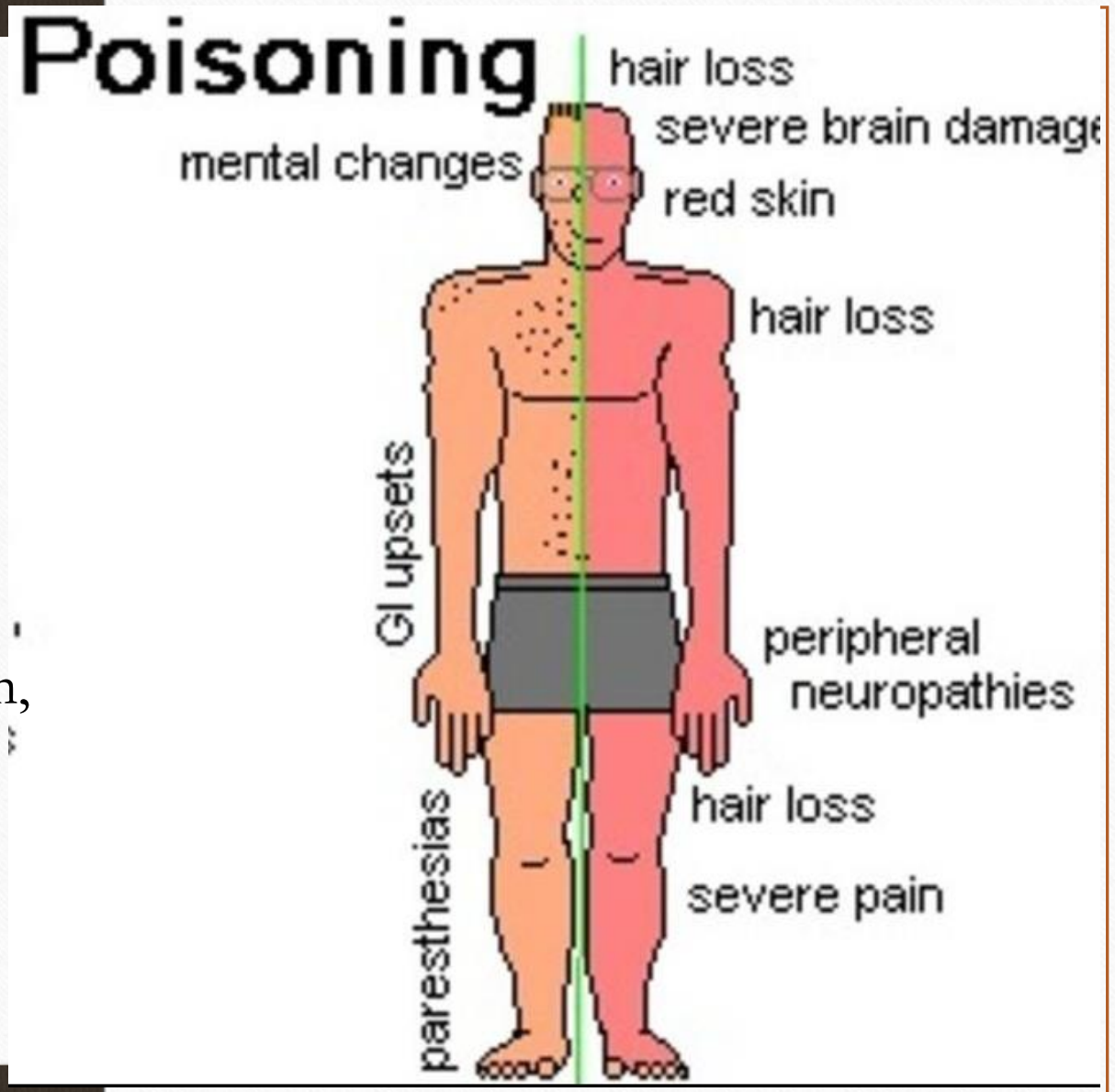
# Rodenticide: Thallium


- Tl inhibits oxidative phosphorylation through its ability to interfere with sulfhydril-containing enzymes



# Thallium

- Acute ingestion : nausea, vomiting, diarrhea, and tremors.
- Neurologically, Tl precipitates a syndrome resembling Guillain-Barre´—that is, acute febrile polyneuritis: agitation, confusion, pain, paresthesias, and weakness of the extremities



# Rodenticide: Thallium

## Clinical management

- **Prussian blue** (potassium ferricyanoferrate) has shown some ability to decrease Tl absorption by forming insoluble complexes with the metal.

- **Potassium chloride** administration also prevents renal Tl reabsorption, thereby reducing blood Tl levels

# Rodenticide: Barium


- Barium (Ba) and its salts are used in the production of electronic components, paints, ceramics, lubricating oils, and textiles; as contrast agents in radiology (sulfate salt)
- Ba interferes with $K^+$ efflux from cells, thereby causing a reduction in extracellular $K^+$
- **Symptoms**: hypokalemia and skeletal and cardiac muscle abnormalities. Myoclonus, muscular rigidity, ventricular arrhythmias, vomiting, and diarrhea
- **Treatment** : **Potassium chloride** administration to treat hypokalemia. **Magnesium sulfate or sodium sulfate** orally to precipitate barium