

## GENERALITIES ON PSYCHOTROPIC DRUGS

- **1) Definition**

A psychotropic substance is a natural or synthetic substance that acts on the psyche, leading to:

- Modification of mental activity and mood
- Modification of the perception of the external world

- **2) Classification**

### **2.1 Psycholeptics: decrease in mental activity**

**a) Nooleptics:** decrease in vigilance, induction of sleep

→ Hypnotics:

- Barbiturates
- Non-barbiturates

**b) Thymoleptics:** action on mood

→ Minor tranquilizers (anxiolytics)

→ Major tranquilizers (neuroleptics)

### **2.2 Psychoanaleptics: stimulation of mental activity**

**a) Nooanaleptics:** stimulation of vigilance, few therapeutic indications

→ Amphetamines

**b) Thymoanaleptics:** stimulation of mood

→ Antidepressants

### **2.3 Psychodysleptics**

- Distortion of mental activity
- Depersonalizing or delirium-inducing substances
- Not medications  
→ Example: LSD

### **2.4 Psychoisoleptics**

- Psychic regulators (mood stabilizers)
- Psycholeptic action (in excitation states)
- Preventive action (in mood disorders)

→ Lithium salts, dipropylacetamide

## HYPNOTICS

- **1) Definition**

A hypnotic is any substance capable of inducing and/or maintaining sleep.

All hypnotics share a **depressant effect on the central nervous system (CNS)** which, depending on the dose, leads to:

- Sedation
- Sleep
- Coma

They have been used for a long time.

Chloral hydrate and barbiturates:

- First hypnotics on the market
- Gradually abandoned due to:
  - Risk of dependence
  - Severity of acute intoxication
- Toxic dose  $\approx$  10 times the hypnotic dose (narrow therapeutic index)

Current hypnotics belong mainly to the **benzodiazepine family**.

- **2) Characteristics of the ideal hypnotic**
- Rapid absorption (10–15 minutes)
- Active for at least 5–7 hours
- Preserves sleep architecture (deep sleep and REM sleep)
- No respiratory depression or memory disorders
- No interaction with other treatments or alcohol
- No rebound insomnia or dependence
- No need for dose escalation
- Maintains good daytime alertness

- **3) Drugs with hypnotic properties**

**a) Non-barbiturate hypnotics**

- Benzodiazepines
- Benzodiazepine-like drugs

**Chloral hydrate:**

- Half-life: 4 minutes
- Rapidly metabolized in the liver into **trichloroethanol** (active metabolite, half-life 8–12 h)
- Sensitizes the myocardium to catecholamines

**Quinolones:**

- Methaqualone (MANDRAX®)

**Others:**

- H1 antihistamines:
  - Hydroxyzine
  - Diphenhydramine
- Sedative neuroleptics (Largactil®, Nozinan®)  
→ Reserved for severe insomnia, often in psychotic patients
- Plants:
  - Valerian extract
  - Lemon balm, hawthorn, linden, passionflower

**b) Barbiturate hypnotics**

- Powerful sedatives
- Slow down the CNS
- Sedative-hypnotic action
- Discovered in 1864 by Fischer and Von Mering

**Examples:**

- Phenobarbital: treatment of major and minor epilepsy
- Used as sleeping pills in the 1950s

**Therapeutic uses:**

- Insomnia
- Anesthesia
- Epilepsy

**Current status:**

- Replaced by benzodiazepines (wider therapeutic index)
- High risk of dependence

## ◆ BARBITURATES

### • I) Physicochemical properties

#### A) Physical properties

- Crystalline
- Colorless
- Odorless
- Slightly bitter taste
- Poorly soluble in water
- Sodium salts are water-soluble

#### B) Chemical properties

- Weak acids
- pKa: 7.2 – 7.9
- Derived from malonylurea
- Substitution at C5 → therapeutic activity
- Substitution at C2 → anesthetic effect

Two forms depending on pH:

- Enolic form
- Ketonic form

### • II) Classification

#### 1. Chemical classification

- Barbiturates substituted at C5
- Veronalides substituted at N1
- Thiobarbiturates substituted at C2

#### 2. Clinical classification

- **Long-acting (8–12 h):** Barbital, Phenobarbital
- **Short-acting (4–8 h):** Pentobarbital, Secobarbital
- **Ultra-short acting (1–4 h):** Thiopental, Hexobarbital

- **III) Pharmacokinetics**

### 1. Absorption

- Oral (most common, especially in poisoning)
- In the stomach: acidic pH → non-ionized, liposoluble form
- Complete absorption in 30 min to 3 hours

Massive ingestion:

- Slower absorption due to intestinal hypomotility in coma
- Delayed absorption (2–3 days)
- Rectal route: faster absorption

### 2. Distribution

- Diffuses into all tissues
- Liposoluble → accumulates in CNS and adipose tissue
- Crosses CSF, placenta, and breast milk

### 3. Biotransformation

- Depends on liposolubility
- Long-acting: little or no metabolism
- Short/intermediate: hepatic metabolism → inactive metabolites

### 4. Elimination

- Mainly urinary
- Long-acting: unchanged ( $t_{1/2} > 18$  h)
- Intermediate:  $t_{1/2} = 6-8$  h
- Short:  $t_{1/2} = 3-4$  h

- **IV) Mechanism of action**

- GABA receptor agonists → increase duration of  $\text{Cl}^-$  channel opening
- Glutamate antagonists

 Result: CNS depression

**Effects:**

- Anticonvulsant
- Sedative
- Hypnotic
- Anesthetic
- Respiratory depression (high doses)

**Other effects**

- Pharmacodynamic tolerance
- Withdrawal phenomena
- Enzyme induction

- **V) Side effects**

**Immediate**

- Ataxia
- Nystagmus
- Respiratory depression
- Cardiovascular collapse

**Chronic use**

- Megaloblastic anemia (folate deficiency)
- Osteomalacia
- Hepatitis
- Increased transaminases and GGT

**Pregnancy**

- Teratogenic risk (minor malformations, neural tube defects – not confirmed)

## **Other risks**

- Neonatal hemorrhage (vitamin K deficiency)
- Withdrawal syndrome (3–15 days):
  - Tremors
  - Irritability
  - Epilepsy
- Drug accumulation in breastfeeding infants
- Possible long-term cognitive effects

- **VI) Toxicity**

At toxic doses:

- Inhibition of mitochondrial oxidative metabolism

Affects:

- Cortex → coma
- Brainstem → respiratory disorders, hypotension
- Spinal cord → decreased muscle tone and reflexes

**LD50 = 10 g**

Higher risk in patients with:

- Respiratory diseases
- Cardiac diseases
- Drug abuse

- **VII) Acute intoxication symptoms**

**CNS**

- Drowsiness
- Dysarthria
- Ataxia
- Confusion
- Coma
- EEG changes

## **Barbiturate coma**

### **Early (within 30 min):**

- Vomiting
- Alcohol-like symptoms
- Deep sleep
- Headache

### **Advanced:**

- Deep areflexic coma
- Hypotonia, hypothermia
- Loss of sensitivity
- Loss of corneal reflex
- Pupils: initially constricted → then dilated

## **Other systems**

- Respiratory depression
- Hypotension, shock
- Skin lesions (bullae, necrosis)
- Rhabdomyolysis

- **VIII) Treatment**

### **a) Symptomatic**

- Assisted ventilation
- Cardiorespiratory monitoring
- Prevention of infections (antibiotics)

### **b) Evacuative**

- Gastric lavage
- Aspiration
- Activated charcoal
- Intubation if coma

### **c) Elimination**

- Alkalinization (glucose, bicarbonates, mannitol)
- Forced diuresis (ineffective)
- Hemodialysis (ineffective)

### **d) Monitoring**

- Electrolytes every 2 hours
- Blood pH
- EEG, ECG

- **IX) Evolution**

- Progressive rise in temperature
- Possible death within 2–3 days

Favorable cases:

- Gradual recovery → complete healing

Possible complications:

- Cardiac
- Pulmonary
- Cutaneous
- Neurological

- **X) Toxicological analysis**

### **Extraction**

- Acidification + organic solvent extraction

Samples:

- Urine (Griffon method)
- Blood (Bourdon and Younger)
- Organs (Stas method)

### **Identification (qualitative)**

- Microcrystallization (Deniges)
- Thin-layer chromatography (Lemaire reagent)

### **Color reactions:**

- Parri reaction → violet color
- Mercury sulfate → white precipitate

### **Quantification**

- Spectrophotometry (depending on pH):
  - Enolic form → strong absorption (260 nm)
  - Ketonic form → weak absorption (238 nm)
- Immunoassay (fluorescence polarization)
- Chromatography:
  - HPLC
  - Gas chromatography