Al-Mustaqbal University
College of Pharmacy
5th stage
Clinical Toxicology
Lecture: 7

Abused Substances Toxicity

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Opioids Toxicity

Opium (Opiates):

- ✓ **Is the air dried milky exudates obtained by incising the unripe capsules of *Papaver somniferum.***
- ✓ **More than 30 different alkaloids have been obtained from opium and its extracts.**
- ✓ **The most important of these are thebaine, codeine and morphine.**

Opioids Toxicity

Opium (Opiates):

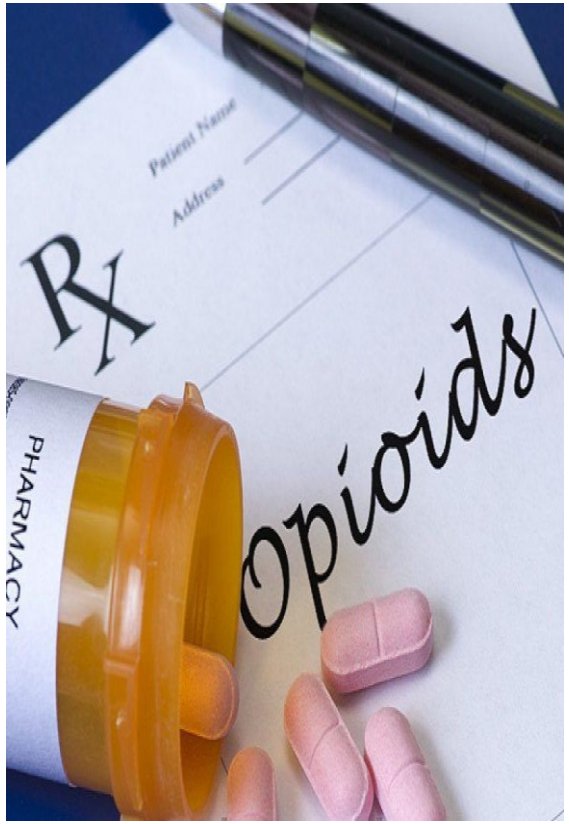
Thebaine → demethylation → **Codeine** → Demethylation → **Morphine**

Morphine → diacetylation → **Heroin** (diacetyl morphine)

Opioids Toxicity

Opioids :

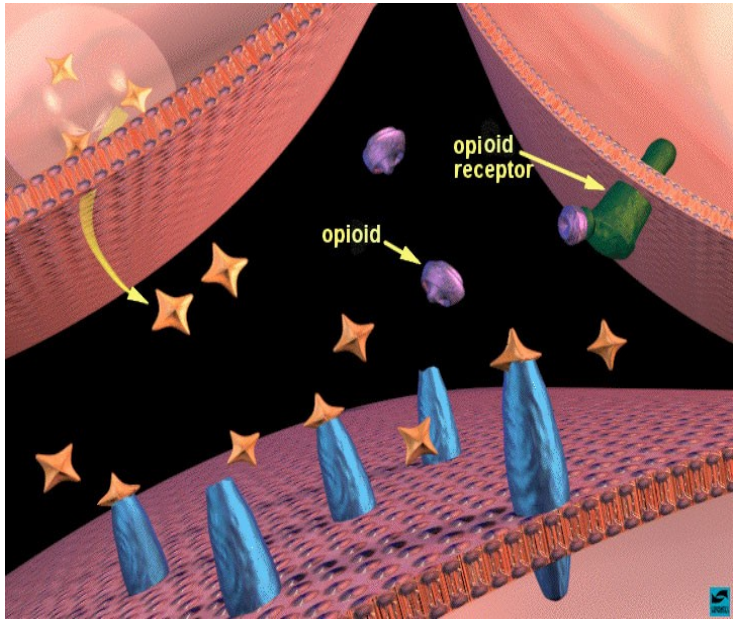
- ✓Refer to **synthetic** morphine like compounds.
- ✓Many of opioids offer the same **narcotic and pain** relieving properties as morphine but **not** as habit – forming.
- ✓Other posses the **cough relieving activity** of codeine but are **not addictive**.
- ✓Opioids include **oxycodone**, **hydrocodone**, and **fentanyl**.



Pathophysiology of Opioids Toxicity

- ✓ **Activation** of opioid receptors results in **inhibition** of synaptic neurotransmission in the central nervous system (**CNS**) and peripheral nervous system (**PNS**).

- ✓ The **physiological** effects of opioids are mediated principally through (**mu**) and (**kappa**) receptors in the CNS and periphery.



Pathophysiology of Opioids Toxicity

(Mu) receptor effects include:

- ✓ **Analgesia, Euphoria, Respiratory Depression, and Miosis.**

(Kappa) receptor effects include:

- ✓ **Analgesia, Miosis, Respiratory Depression, and Sedation.**

Pathophysiology of Opioids Toxicity

- ✓**Two other opioids receptors that mediate the effects of certain opiates include (sigma) and (delta) sites.**
- ✓**Sigma receptors mediate dysphoria, hallucinations, and psychosis.**
- ✓**Delta receptor agonism results in euphoria, analgesia, and seizures.**
- ✓**The opioid antagonists (eg, naloxone, nalmefene, naltrexone) antagonize the effects at all 4 opioid receptors.**

Pathophysiology of Opioids Toxicity

- ✓ **Common classifications divide the opioids into:**
  1. **Agonist agents**
  2. **Partial agonist agents**
  3. **Agonist-antagonist agents**
- ✓ **Also, opioids can be classified as natural, semisynthetic, or synthetic.**
- ✓ **Opioids decrease the sensitivity to pain, rather than eliminate or reduce the painful stimulus.**
- ✓ **Additionally, it can induce slight euphoria.**

Pathophysiology of Opioids Toxicity

- ✓The GI tract and the respiratory mucosa provide easy absorption for most opioids.
- ✓Peak effects generally are reached in
- ✓ 10 minutes with the intravenous route,
- ✓ 15 minutes after nasal inhalation,
- ✓30 minutes with the intramuscular route,
- ✓90 minutes with the oral route, and 2-4 hours after dermal application.

Pathophysiology of Opioids Toxicity

- ✓Following therapeutic doses, most absorption occurs in the small intestine.
- ✓Toxic doses may have delayed absorption because of delayed gastric emptying and slowed gut motility.
- ✓Most opioids are metabolized by hepatic conjugation to inactive compounds that are excreted readily in the urine.
- ✓Certain opioids are more lipid soluble and can be stored in the fatty tissues of the body.

Pathophysiology of Opioids Toxicity

- ✓**Methadone, a long-acting narcotic often used to attenuate withdrawal symptoms and used in narcotics recovery programs,**
- ✓**Also it has extensive potential for abuse.**
- ✓**It can be ingested orally or pills can be crushed and used intravenously or intranasally.**

Signs & Symptoms of Opioids Toxicity

- ✓Opioid toxicity characteristically presents with a depressed level of consciousness.
- ✓Opiate toxicity should be suspected when CNS depression, respiratory depression, and pupillary miosis are present.
- ✓It is important for the clinician to be aware that opioid exposure does not always result in miosis (pupillary constriction) and that respiratory depression is the most specific sign.
- ✓Drowsiness and euphoria are seen frequently.

Signs & Symptoms of Opioids Toxicity

- ✓**Needle tracks** are observed occasionally, depending on the **route of abuse**.
- ✓**Street users** commonly use **heroin** and **morphine** by **subcutaneous** and **intravenous** injection.
- ✓**Raw opium** usually is eaten or smoked, and sometimes the powder is **sniffed**.

Signs & Symptoms of Opioids Toxicity

- ✓Other important presenting signs are ventricular arrhythmias, acute mental status changes, and seizures.
- ✓Reliance on pupillary miosis to diagnose opioid intoxication can be misleading.
- ✓If sufficiently severe, hypertension and pupillary dilation may present because of CNS hypoxia.
- ✓Morphine, meperidine, pentazocine, diphenoxylate, and propoxyphene sometimes are associated with mydriasis or midpoint pupils.
- ✓Both bradypnea and hypopnea are observed, rates as slow as 4-6 often are observed with moderate-to-severe intoxication.

Signs & Symptoms of Opioids Toxicity

- ✓Mild peripheral vasodilation may occur and result in orthostatic hypotension.
- ✓Opioids prolong GI transit times, possibly causing delayed and prolonged absorption.
- ✓Initial tendencies for nausea and emesis are transient.
- ✓Pink frothy sputum, muscular rigidity, dyspnea, hypoxia and bronchospasm strongly suggest acute lung injury.

Signs & Symptoms of Opioids Toxicity

- ✓Nightmares, anxiety, agitation, euphoria, dysphoria, depression, paranoia, and hallucinations are encountered infrequently, mainly with high doses.
- ✓Pruritus, flushed skin, and urticaria may arise because of histamine release.
- ✓Generalized seizures are infrequent; they occur most commonly in infants and children because of initial CNS excitation.
- ✓In contrast, seizure activity in adults is suggestive of meperidine or propoxyphene ingestions.
- ✓Hearing loss has been associated with heroin and alcohol but is generally considered recoverable.

Management of Opioids Toxicity

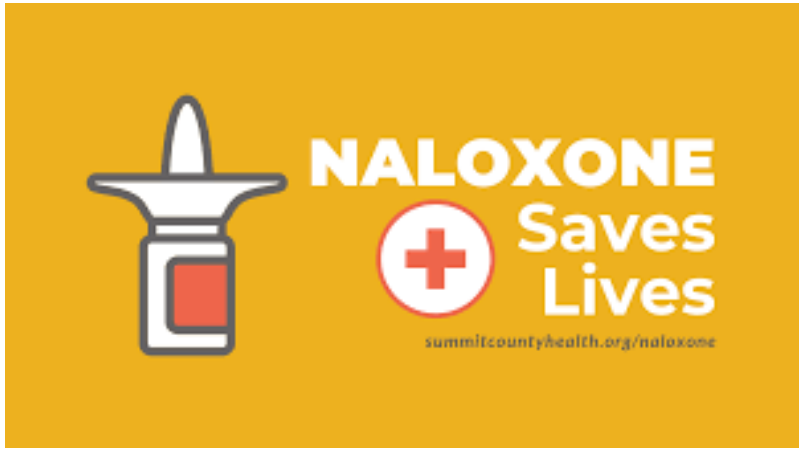
- ✓**Death** following opioid overdose is **preventable** if the person receives **basic life support** and the timely administration of the drug **naloxone**.
- ✓Naloxone is an **antidote** to opioids that will **reverse** the effects of an opioid overdose if administered in time.
- ✓Naloxone has virtually **no effect** in people who have **not taken opioids**.

Management of Opioids Toxicity

- ✓In many countries there is still limited availability of naloxone even in medical settings, including in ambulances.
- ✓On the other hand, some countries have already made naloxone available in pharmacies without prescription.
- ✓Several countries (Australia, Canada, Italy, the United Kingdom of Great Britain and Northern Ireland and Ukraine) have introduced naloxone as over-the-counter medication and have also started proactive dissemination in communities.

Management of Opioids Toxicity

- ✓**Naloxone** is a **competitive antagonist** of opioid receptors and lacks **any agonist** activity.
- ✓Adverse effects are **rare** at therapeutic doses.
- ✓Naloxone can be given **IV, IM or intranasal**.

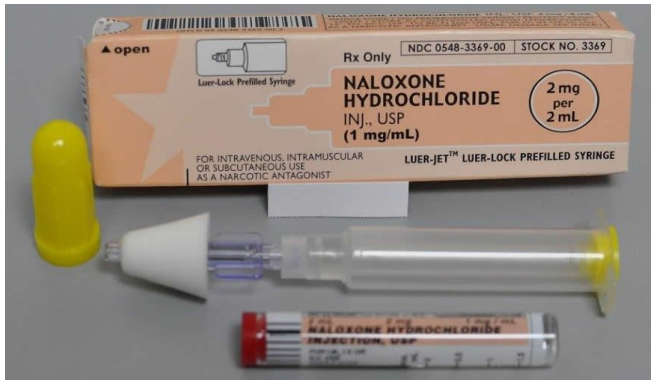


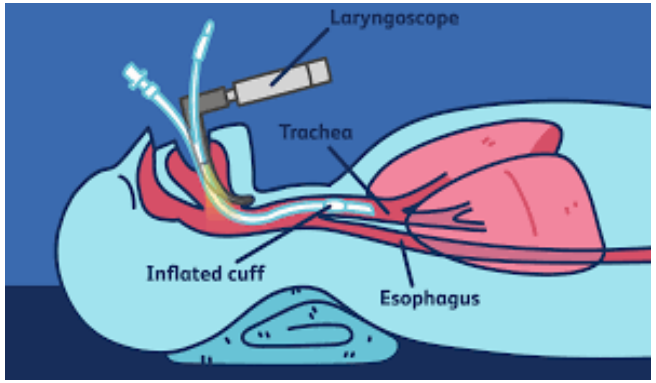
Management of Opioids Toxicity

- ✓**Nalmefene** and **naltrexone** are other opioid antagonists that have **longer** half-lives than naloxone.
- ✓The **routine use** of a long-acting antagonist in the patient who is unconscious for **unknown** reasons is **not recommended**.
- ✓In addition, the fear of **precipitating** prolonged opioid **withdrawal** likely prevents the widespread use of these antagonists for **emergency** reversal of **opiate** intoxication.

Management of Opioids Toxicity

- ✓In patients lacking spontaneous respirations, intubation is preferred, and intravenous naloxone may be given to reduce respiratory depression.
- ✓Airway control and adequate oxygenation.
- ✓As with all unknown unconscious patients, determination of serum glucose level is required.





Management of Opioids Toxicity

- ✓Activated charcoal is the GI decontamination method of choice for patients with opiate intoxication following ingestion.
- ✓Because of impairment of gastric emptying and GI motility produced by opiate intoxication, activated charcoal still may be effective when patients present late following ingestion.
- ✓Decontamination with activated charcoal should be attempted in all symptomatic patients (as long as it is not contraindicated), regardless of the time of ingestion in relation to hospital presentation.
- ✓Airway has to be protected prior to administration of charcoal in order to prevent charcoal lung aspiration.

Lysergic Acid Diethylamide (LSD) Toxicity

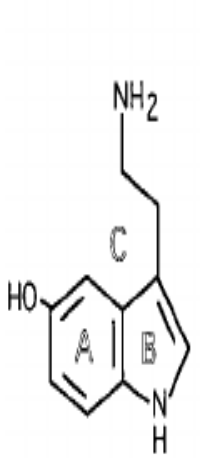
- ✓**LSD is one of the most potent psychoactive compounds was used as a psychotherapy in 1950's.**
- ✓**An oral dose of 25 µg is capable of producing potential psychological effects.**
- ✓**The drug is odorless, colorless, and slightly bitter tasting and water-soluble substance.**
- ✓**It is usually taken by mouth and rapidly absorbed by the gastrointestinal tract.**
- ✓**LSD toxicity can lead to respiratory arrest, coma, emesis, hyperthermia, autonomic instability, and bleeding disorders.**

Lysergic Acid Diethylamide (LSD) Toxicity

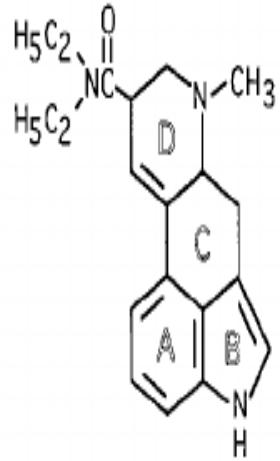
- ✓**LSD causes changes in thought, mood, and perception, with minimal effects on memory and orientation.**
- ✓**The drug primarily produces pseudohallucinations. True hallucinations occur as well; visual hallucinations are the most common.**
- ✓**In general, hallucinogens can intensify the patient's current mood; pleasant feelings can be augmented to euphoric ones, with an expanded consciousness.**
- ✓**Negative feelings or depressive symptoms can be amplified to a dysphoric experience.**

LSD Pathophysiology

- ✓The **most common route** of exposure to LSD is **oral**; the drug is absorbed **rapidly** from the **GIT**.
- ✓**Because of their structural similarity to serotonin and their intrinsic potency, hallucinogens disrupt the balanced functioning of the serotonin system.**
- ✓**Hallucinogens have a high affinity for serotonin**
- ✓**(5-HT) receptors, at which LSD exhibits agonist and antagonist properties.**



5-HT



LSD

LSD Pathophysiology

- ✓**The 5-HT2A receptor plays a major role in the modulation of sensory signals of the prefrontal cerebral cortex, where hallucinogens have effects on cognition, mood, perception, and emotions ranging from fear to euphoria.**
- ✓**These receptors are also thought to be responsible for the pathology and therapy of schizophrenia.**

LSD Pathophysiology

✓**Serotonin receptors** also important for **sensory modulation** and are **responsible** for the **sympathomimetic effects** of the drug (hypertension, tachycardia, dizziness, loss of appetite, dry mouth, sweating, nausea, numbness, tremor).

✓LSD also **stimulates dopamine (D2) receptors**, this leads to a **biphasic** pharmacologic pattern of :

1. **Early serotonin like effects** (15-30 min after administration)
2. **Late mediated dopamine like** effects (60-90 min after administration).

LSD Toxicity Management

- ✓The basic rule of management is reassurance in a safe, calm and stress-free environment.
- ✓Rarely, patients need to be either sedated or physically restrained.
- ✓Benzodiazepines can safely be given to treat agitation.
- ✓Massive ingestions of LSD should be treated with supportive care, including respiratory support and endotracheal intubation if needed.

LSD Toxicity Management

✓**The following should be treated symptomatically:**

1. **Hypertension**
2. **Tachycardia**
3. **Hyperthermia**
4. **Hypotension - Should be treated initially with fluids and subsequently with pressors if required**

Cannabinoids Toxicity

Cannabinoids Toxicity

- ✓ ***Cannabis sativa*** **is the plant from which marijuana and cannabinoids are derived.**
- ✓ **The most potent form of this plant's extracts is hash oil (a liquid).**
- ✓ **The dried flowers tops and leaves are smoked as a cigarette.**

Cannabinoids Toxicity

- ✓More than **400 active compounds** have been isolated from the *Cannabis sativa* plant.
- ✓**Sixty active compounds** are unique to the plant and are collectively known as **cannabinoids**.
- ✓**Delta-9-tetrahydrocannanbinol** (THC) is the most **psychoactive** cannabinoid, producing euphoria, relaxation, diminished pain, and difficulties with memory and concentration.

Cannabinoids Toxicity

✓**Cannabis is available in the following forms:**

1. **Marijuana is a combination of the *Cannabis sativa* flowering tops and leaves, the THC content is 0.5-5%.**
2. **Hashish is dried resin collected from the flowering tops, the THC concentration is 2-20%.**
3. **Hash oil is a liquid extract; it contains 15% THC.**
4. **Sinsemilla is without seedd - unpollinated flowering tops. THC content is as high as 20%.**
5. **Dutch hemp (Netherwood) has a THC concentration as high as 20%.**

Cannabinoids Absorption

- ✓ **The route of administration determines the absorption of the cannabis product.**
- ✓ **Smoking – Onset of action is rapid (within minutes); it results in 10-35% absorption of the available THC; peak plasma concentrations occur within 8 minutes.**
- ✓ **Ingestion – Onset occurs within 1-3 hours; 5-20% is absorbed due to stomach acid content and metabolism; peak plasma levels occur 2-6 hours after ingestion.**

Cannabinoids Toxicity Pathophysiology

- ✓**The specific cannabinoid receptors were discovered, CB1 and CB2.**
- ✓**The CB1 receptors are predominantly located in the brain areas responsible for anxiety, pain, sensory perception, motor coordination, memory, movement and endocrine function. This distribution is consistent with the clinical effects obtained by cannabinoids.**
- ✓**The CB2 receptor, is located peripherally. Specifically, it is involved in the immune system (macrophages, T and B lymphocytes), peripheral nerves.**

Cannabinoids Toxicity Pathophysiology

- ✓**Both the CB1 and CB2 receptors inhibit adenylate cyclase and stimulate potassium channels. (endocannabinoid system)**
- ✓**As a result, the CR1 receptors inhibit the release of several neurotransmitters, including acetylcholine, glutamate, norepinephrine, dopamine, serotonin, and gamma–aminobutyric acid (GABA).**
- ✓**CR2 receptor signaling is involved in immune and inflammatory reactions.**

Signs and symptoms of Cannabinoids Toxicity

Behavioral effects:

- ✓**THC produces euphoria, relaxation, laughter, talkativeness, decreased anxiety, decreased alertness, and depression.**
- ✓**<u>These effects depend on the dose and mode of administration.</u>**

Mental effects:

- ✓**Short-term memory is impaired.**

Signs and symptoms of Cannabinoids Toxicity

Cardiovascular effects:

- ✓ **Rise in heart rate, lasting up to 2-3 hours.**
- ✓ **Peripheral vasodilatation causes postural hypotension, which may lead to dizziness or syncope.**
- ✓ **Cardiac output increases by as much as 30%**
- ✓ **In addition, the cardiac oxygen demand is also increased.**
- ✓ **Tolerance to these effects can develop within a few days of use.**

Signs and symptoms of Cannabinoids Toxicity

Immune system effects:

- ✓ **Cannabis use can impair the immune system's ability to fight microbial and viral infection.**

Psychosis association:

- ✓ **Large doses of THC may produce confusion, amnesia, delusions, hallucinations, anxiety, and agitation.**

Treatment of Cannabinoids Toxicity

- ✓**Immediate management should be supportive, including cardiovascular and neurological monitoring, and placement in a quiet room.**
- ✓**Gastric decontamination may be considered with an acute ingestion less than 2 hours prior to presentation.**
- ✓**Patients who are agitated or with psychosis should be treated with benzodiazepines.**

THANK YOU
FOR YOUR ATTENTION