بسم الله الرحمن الرحيم

Pharmacology of addiction
Drugs and substances of abuse
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Drugs

Drug is a term used in **different ways.**

➤ In medicine, drugs are used to diagnose, prevent or control (cure or palliate) diseases or enhance physical or mental welfare or prevent pregnancy.

➤ In pharmacology, a drug (**chemical agent**) that alters a biological system.

➤ **In the field of addiction**; "drug" means any of the substances listed in Schedule I and II (of 1961 Single Convention on Narcotic Drugs, whether natural or synthetic).

Licit versus illicit drugs

➤ The word **licit** means within the law (legal to purchase & use).

➤ Licit drugs include caffeine, nicotine & alcohol (forbidden in some countries).

➤ These drugs can be abused & addicted but still licit ones.

➤ Legal drug use includes also prescription drugs that are used according to doctor's instruction as well as by the person for whom (Over the counter use).

➤ On the other hand; illicit drugs refer to drugs that are illegal (forbidden) to use, to sell and to make (e.g., cocaine, marijuana and heroin).

Prescription drug abuse (misuse)

It is the use of a <u>prescribed medication</u> in a way other than as prescribed, or for the experience or feelings elicited.

Prescription medications (e.g., opiates to treat pain, amphetamine for attention deficit disorders and benzodiazepines for anxiety) are now abused at a rate second only to marijuana among illicit drug users.

Example of scheduled drugs in USA

Schedule I: High abuse potential, no accepted medical use (e.g., Heroin, LSD, Marijuana, and Ecstasy).

Schedule II: High abuse potential or medical use with severe restrictions, e.g., Cocaine, Methamphetamine, Oxycodone, Adderall (amphetamine-dextroamphetamine) & Ritalin (methylphenidate)

Schedule III: Moderate abuse potential (e.g., Codeine, Ketamine, Anabolic Steroids).

Schedule IV: Lower abuse potential (e.g., benzodiazepines, Tramadol).

Schedule V: Lowest abuse potential (e.g., antidiarrheal (Lomotil), antitussive & analgesic (containing codeine), and pregabalin).

National institute of drug abuse (NIDA) definitions

➢ **Drug abuse**: The **use** of **illegal drugs** or the inappropriate use of prescription drugs (**misuse**)

➢ **Drug dependence**: A physiological state after prolonged drug use; whereby abrupt discontinuation of a drug will result in **withdrawal symptoms**.

➢ **Drug addiction**: a chronic **disorder** that is characterized by **compulsive drug seeking** and **use**, despite known harmful consequences.

➢ *If addiction occurs, dependence always exists.*

Dependency vs. Addiction

	Dependency	Addiction
Withdrawal Symptoms	✓	✓
Physical Dependence	✓	✓
Psychological Dependence		✓
Unable to stop using drugs		✓
Uses drugs despite consequences		✓

Physical (physiological) dependence

Dependence (physical dependence) is related to the physical or **physiological adaptation** of the body to the presence of the drug for long periods, tolerance usually occurs with chronic use. Withdrawal of the drug results in manifestations called **abstinence** or **withdrawal syndrome**.

❑ Dependence can occur with some drugs prescribed for a variety of diseases (e.g. corticosteroids, beta blockers and nitrates) which are **not addicted.**

❑Dependence occurs with all drugs & substances addicted (e.g. alcohol & opioids).

Example:there is no known addiction beta blockers, but addiction exists with opioids, however both beta blockers and opioids had dependence.

Example of withdrawal syndromes associated with dependence:
  ➢Sudden withdrawal of **beta blockers** can result in **palpitations** & **angina**.
  ➢Sudden withdrawal of corticosteroids can lead to relapse of the treated disease (rheumatoid arthritis flare) and suppression of adrenal axis.
  ➢Sudden withdrawal of **benzodiazepines** produce **insomnia**, **anxiety** and rarely **seizures**.

Psychological dependence (addiction)

❑**Addiction (psychological dependence)** is a **psychological drug seeking behavior**.

❑Addiction is marked by a <u>change in behavior</u> caused by the biochemical changes in the brain after continued substance abuse.

❑Substance or drug use becomes the **first priority** of the addict, **regardless of the harm** they may <u>cause to themselves or others</u>.

❑**Addiction** is <u>not</u> an <u>acute</u> <u>illness</u> like fracture or bacterial infection, it is **chronic relapsing disease** with brain changes involving the neurochemistry, neurophysiology and even the structure of the brain).

❑The addict's brain differs from non-addict's one and **treating CNS disorders** may be **<u>altered by the presence of addiction</u>** in a given individual.

Classification of drugs of abuse

❑Substances & drugs commonly abused are usually classified on basis of their pharmacological effects on the CNS (*stimulants*, *sedatives*, *hallucinogens*, *analgesics*) or their pharmacological target (drugs acting on inotropic or metabotropic receptors, drugs acting on neurotransmitter transporters and drugs acting on ion channels).

❑Other classifications based on the route of administration (*injectable* drugs, *oral*, *smoking*, *inhalation*)

❑Classifications based on their addictive potential or relative risk of addiction where *cocaine and amphetamine* are *highly addictive* drugs *(relative risk=5)*, followed by *opioids* and *nicotine* *(relative risk=4)*, followed by *alcohol* and *hypnotics (relative risk=3)*, followed by *cannabinoids (relative risk=2)*, and *hallucinogens* including ketamine *(relative risk=1)*.

relative risk of addiction; 1 = least-addictive; to 5 = extremely addictive.

Major drugs and substances of abuse

1-**CNS depressants**: Alcohol (ethanol), barbiturates and benzodiazepines.

2-**CNS Stimulants**: Cocaine (crack), nicotine , amphetamine & its derivatives including ecstasy. Tricyclic antidepressants also stimulate CNS

3-**Hallucinogens** :magic mushrooms, lysergic acid diethylamide (LSD) and club drugs.

4-**Opioids**: Crude opium, morphine, codeine, heroine, tramadol and others.

5-**Inhalants:** paint, glue, gasoline, acetone, gases (e.g. nitrous oxide) and others.

6- **Cannabis**: a plant-derived drug that is the most commonly used illicit drug worldwide. Cannabis is abused in various forms including hashish.

7- **New psychoactive substances**: **synthetic cannabinoids** and **cathinones**, **ketamine**, **piperazines**, & some plant-based drugs such as **khat and kratom.**

8- **Miscellaneous**: e.g. anabolic **steroids**, **trihexaphenidyl** and **pregabalin**.

Patterns of drug/substance abuse

1 _Experimental use_: a person's exploration for the **first time**.

2 _Occasional use_ : It describes the use of drugs or alcohol _socially_.

3 _Situational use_: It describes the use of drugs or alcohol specific to a situation. For example, the use of _amphetamines_ prior to school _exams_ by students.

4- _Regular use_: a **heavier**, **more frequent** and/or more **harmful/risky use.**

5-_Dependent use (Abuse)_: It describes the difficulty to control or stop the use of alcohol or drugs, withdrawal symptoms occur when not using the drug or alcohol.
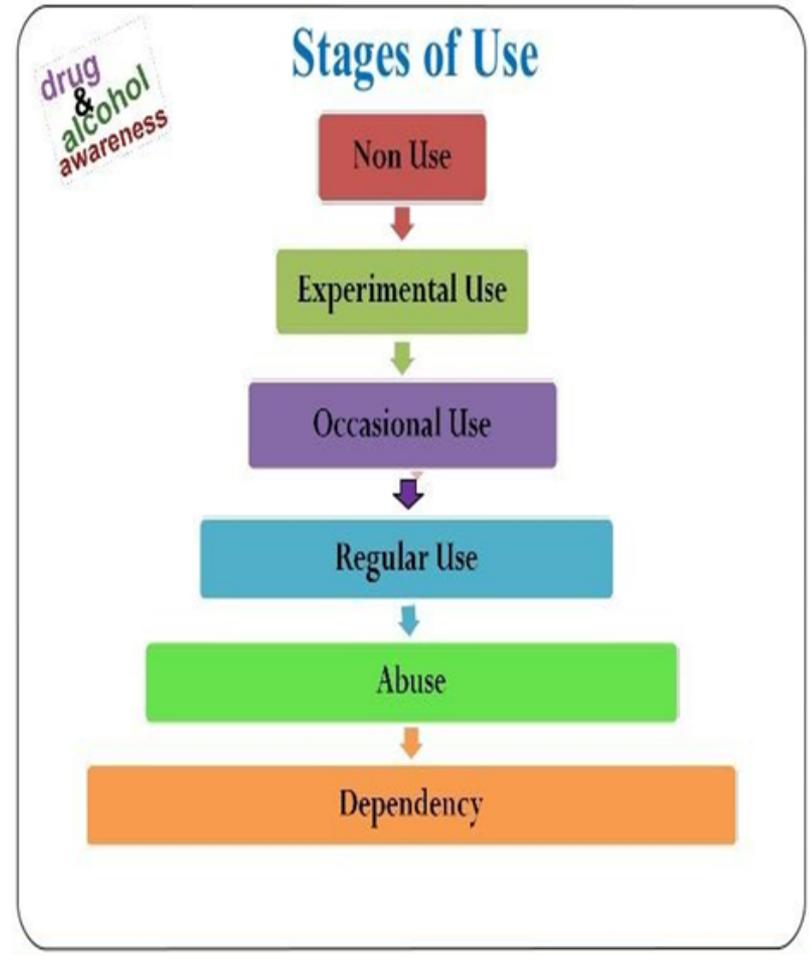
Factors affecting substance and drug abuse

1- Gender: Males are **three times more** likely than females to abuse cannabis, cocaine & amphetamines, However females are more likely to abuse prescription drugs (e.g., opioids and tranquilizers).

2- Age

➢Drug abuse is more common among **young** (teen agers and mid-20s).

➢Early (12 to 14) to late (15 to 17) adolescence is a critical risk period for the initiation to use *alcohol, marijuana,* and *inhalants*.

➢ The risk of developing dependence or addiction is greater for individuals who initiate use of these substances in adolescence than adulthood.

➢The prefrontal cortex and its connections to other brain regions remains *incompletely developed* during the teen years.

➢The prefrontal cortex is responsible for **assessing situations**, **making sound decisions**, and **controlling the emotions and impulses**; typically, this circuitry (*which can resist addiction behavior*) is **not mature** *until* a person is in the mid-20s (age **of 25 year old**)

3-Socioeconomic factors

❑High and low socioeconomics are related to different drug abuse

4- Risk factors (Personal susceptibility, host and drug factors)

Genetic factors account for 40-60 % of a person's liability for addiction; this includes the effects of **environmental factors** on the function and expression of a person's genes.

Drug factor:

- Method of Administration.
- Cost and availability.
- Effects of the drug itself.

Addiction & health

Addiction can be complicated by:

1. Cardiovascular disease.
2. Stroke.
3. Cancers.
4. HIV/AIDS.
5. Hepatitis B and C.
6. Lung disease and tuberculosis.
7. Mental disorders such as depression.
8. Liver cirrhosis.
9. Acute and chronic toxicity.
10. Increase risk of accidents, suicide and homicide.

Neurological Hypotheses of abuse

1- The dopamine reward system

▪ Substances & drugs of abuse ↑ **dopamine** in the nucleus accumbens (part of the **reward** system or pleasure center).

▪Nucleus accumbens receives input from the ventral tegmental area (VTA) in the midbrain.

▪**Dopamine levels** ↑ in **addicts** (this is accompanied with down regulation and decrease the number of D2 receptors); this will **enforce** addicts to continue drug use to get the same previous effects.

▪During **withdrawal** the reverse occurs; **dopamine levels decrease** and D2 receptors start to increase

▪Dopamine pathway is involved in reinforcement and drug-seeking behavior.
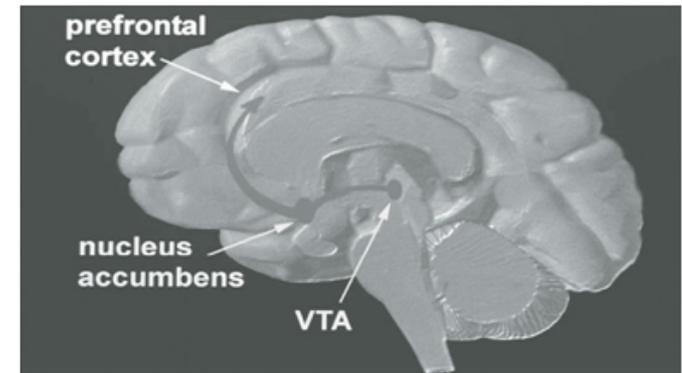
❑Opioids, nicotine and alcohol **block the inhibitory control** of GABA on the VTA leading to an ↑ firing of neurons to the nucleus accumbens.

❑Cocaine and amphetamines (psychomotor stimulants) act directly on the nucleus accumbens, **blocking the reuptake of dopamine**.

2. Endogenous opioid system

❑ The opioid system may be involved in the **rewarding effects** of exogenous opiates (opioid drugs & crude opium) & other substances (e.g., alcohol, cannabinoids and tobacco)

❑ Naltrexone (opioid antagonist) can block the reinforcing properties of alcohol, suggesting that role of endogenous opioid system in the rewarding effects of alcohol and justify the use of **Naltrexone** for treating alcohol dependence.

❑ Long-term **tobacco** smoking may cause changes in the functions of the endogenous opioid system, which leads to an nicotine dependence.

3 –Glutamate

➢ Glutamate plays an important role in dependence and addiction.

➢ **NMDA blockers (e.g., topiramate)** are used now for treating drug & substance abuse and dependence.

Reinforcement and neuro-adaptation in addiction

Reinforcement: when a stimulus (e.g., the drug itself or drug withdrawal) increases the probability of a response (e.g., continued use of the drug or drug seeking behavior).

❑**Positive reinforcement** like euphoria, excitation and help sleep.

❑**Negative reinforcement** like removing anxiety, pain and insomnia.

Neuro-adaptation: the changes in the brain that occur to oppose a drug's actions after repeated administration. This hypothesis can explain tolerance to the effects of a drug, withdrawal when drug administration stops and relapse.

➢When drugs are repeatedly administered, changes occur in the neurochemistry and neurophysiology of the brain to **oppose** the drug's effects (**tolerance** occur) and reach a state of homeostasis.

➢When this drug use is **discontinued**, the adaptations are no longer opposed; the brain's homeostasis is disrupted and **withdrawal manifestations** occur.

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➤ The **dopaminergic pathway** → **preparatory** aspects of reward (**motivation**), experienced as **thrill** (**sudden excitement & pleasure**), **urgency**, or **craving**.

➤ In contrast, **the opioid system** → **final aspects** of reward & **satiation (fully satisfied)** such as **rest, blissfulness, and sedation.**

Diagnosis and treatment of drug addiction

➢ Drug addiction can be diagnosed **clinically** and **laboratory**.

➢ Some drugs of abuse give characteristic symptoms and signs.

➢ Drug abuse and addiction can **mimic other neurological or psychiatric diseases**.

➢ **Detection** of drugs and substances in the **patients' blood or urine** or other fluids (e.g. oral fluid) or tissues can confirm the diagnosis of drug intake but **cannot confirm addiction or absence of other diseases.**

➢ **Treatment of addiction is complex:** psychological support & monitoring are required

➢ **Different drugs could have a role the treatment of addiction.**

➢ Abusers of drugs and substances could be diagnosed accidently on routine examination (for drivers, students, jobs, military services, etc.)

➢ Addicts may be presented to health care professional complaining of:

1. **Withdrawal manifestations.**

2. **Acute or chronic toxic manifestations.**

3. The person is **requesting help for addiction**.

4. Presenting with **complications from substance abuse**.

Symptoms of Addiction

1. Tolerance → 2. Withdrawal → 3. Loss of control

6. Use despite harm ← 5. Neglect of life ← 4. Inability to stop

Signs of Addiction

3. Increase intake

2. Obsession

1. Tolerance

4. Loss of control

5. Abuse despite harm

6. Withdrawal symptoms

Treatment of drugs and substance abuse

1- **Pharmacological** (i.e., using drugs) treatment.

2- **Psychological** (behavioral) treatment.

3- **Both** pharmacological and psychological approaches.

Pharmacological treatment of drug and substance abuse

1-Withdrawal: Medications help suppress withdrawal symptoms **during detoxification**. Detoxification is only **the first step in the withdrawal process**. Patients who do not receive any further treatment after detoxification could relapse.

2- Relapse prevention: Medications which help in restoring normal brain function and decrease cravings for drugs and substances of abuse.

These medications are available for treatment of opioid (heroin, prescription pain relievers), tobacco (nicotine), and alcohol addiction.

Till now, no drug is approved to treat stimulant (cocaine, methamphetamine) or cannabis (marijuana) addiction.
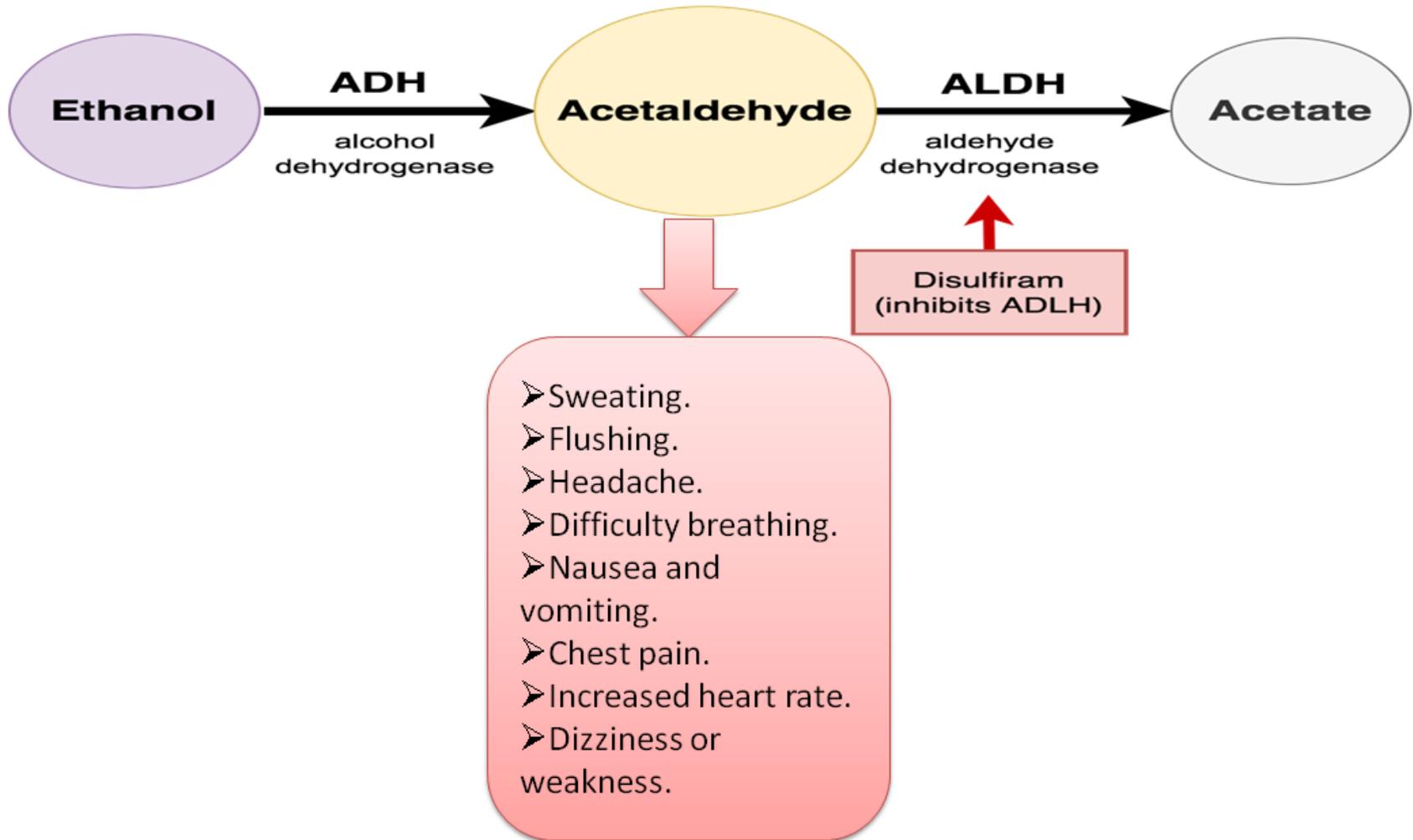
Addiction to prescription stimulants & illicit stimulants like cocaine, can be treated with **behavioral therapies,** as there are not yet medications for treating addiction to these drugs.

3- Treating co-morbidities: such as depression or anxiety that may be contributing to the person's addiction.

Some medications used for treating drug abuse

1. Methadone, buprenorphine used to detoxify opioid addicts.

2. Opioid antagonists (e.g., oral Naltrexone) are used to decrease craving for opioids (in ex-abusers of opioids) and for nicotine and alcohol abuse.

3. Nicotine preparations (patches, gum, lozenges, and nasal spray) and drugs (varenicline (nicotinic partial agonist) and bupropion (antidepressant drug) are used in managing tobacco addiction.

4. Disulfiram, acamprosate (modify glutamate), and naltrexone are medications available for treating alcohol abuse. Topiramate is sometimes prescribed (off-label) for this purpose for alcohol dependence.

5. Clonidine can ↓withdrawal manifestation of alcohol, opioids and nicotine.

6. Treatments for prescription drug abuse tend to be similar to those for illicit drugs that affect the same brain systems.

METABOLISM OF ALCOHOL

Ethanol → **ADH** alcohol dehydrogenase → **Acetaldehyde** → **ALDH** aldehyde dehydrogenase → **Acetate**

Disulfiram (inhibits ADLH)

> Sweating.
> Flushing.
> Headache.
> Difficulty breathing.
> Nausea and vomiting.
> Chest pain.
> Increased heart rate.
> Dizziness or weakness.