Pharmacokinetics & Metabolism:

- water-miscible molecule, **completely absorbed from GIT**
- Peak blood ethanol concentration after **po(Oral)** doses: **30 -75 min, absorption is delayed by food .**
- Volume of distribution = Total Body Water.

1- Oxidation of ethanol to acetaldehyde via

A- **ADH**; reduction of **NAD^+ to NADH**. ***Mainly in liver***.
B- B- Microsomal **ethanol oxidizing system**

2- Acetaldehyde is converted to acetate via AlDH, which also reduce NAD^+ to NADH. (Acetate ultimately is converted to CO_2 + water.**)**

Acute Ethanol intoxication

- **CNS depression**: sedation, relief anxiety, **higher conc.**: slurred speech, ataxia, & impaired judgment
- **Respiratory depression** leading to **respiratory acidosis & coma**
- **Death** can occur from respiratory depression + aspiration of vomitus.
- Significant depression of myocardial contractility
- **Vasodilatation** due to depression of vasomotor center & direct smooth muscle relaxation caused by acetaldehyde.
- **Volume depletion, hypothermia & Hypotension**
- **Hypoglycemia**

Chronic Ethanol consumption:

1- Induces **cytochrome P450,** leads to generation of **ROS**(reactiove oxygen species) **& RNS**(reactive nitrogen species) + hypoxia.
2- Decrease **NAD & increase NADH** by Liver.
3- Accumulation **of acetaldehyde**. (Associated with the '**flushing reaction'** immediately following alcohol intake ,due to increased acetaldehyde in some individuals)
4- **alcohol intrauterine growth retardation**, congenital malformation & teratogenicity.
5-**Gastritis & ulcer diseases**
6-Cancer (tongue, mouth, oropharynx, esophagus, liver, & breast).
7-Pancreatitis.
8- Brain Damage**(Wernicke-Korsakoff syndrome**
First three effects will result in :
-DNA damage, hepatocyte injury & liver disease.
-acidosis & hypoglycemia in **malnourished alcoholics**
-hyperuricemia -Anemia
-Cardiomyopathy; **arrhythmia & HTN.**
-Liver failure & death within 10 yrs.

For adjunctive Treatment of alohol dependence: Disulfiram an Aldehyde dehydrogenase inhibitor.

Alcohol

Alcohol & the neurotransmitters

-Alcohol inhibits NMDA-glutamate (excitatory) Receptors & activates GABAA(Sedative effect & CNS depression Impairment in memory, consciousness, alertness & learning)
-Chronic use of alcohol leads to UP-REGULATION of NMDA-Receptors & voltage-sensitive Ca Channels;
1- Increased NMDA activity significantly increase Ca influx to nerve cells, Ca excess can lead to cell toxicity & death.
2- contributes to **alcohol tolerance** & **withdrawal** symptoms.

Acute Effect of Alcohol on Brain:

- **enhances** the excitatory action of **5-HT** & acetylcholine at **$5\text{-}HT_3$ & nicotinic acetylcholine** receptors (NAch).
- **inhibit** the action of NMDA at glutamate Receptors, **inhibit** voltage-sensitive Ca^{2+} channels & **enhance** the action of **GABA** at inhibitory **$GABA_A$** receptors
- Feelings of **euphoria & the 'high'** often associated with acute alcohol consumption.

Enhances the release of:
-Dopamine directly in **VTA** & indirectly in **NAC**
- **Serotonin:** alcohol rewarding effects, tolerance & withdrawal
-Opioid peptides; feeling of euphoria & increase rewarding effect of alcohol.

Tolerance & Withdrawal

***-Metabolic tolerance*, hepatic enzyme induction** (Microsomal ethanol-oxidizing system)
-Functional tolerance, change in CNS sensitivity (Neuroadaptation); involve **NMDA R, GABA R, 5HT, DA** in brain that lead to reward & reinforcement.
Alcoholism withdrawal Symptoms:

- ✖ Autonomic hyperactivity e.g. cold sweaty skin or **pulse> 100** & craving for alcohol
- ✖ Hand tremor
- ✖ Insomnia, anxiety, agitation
- ✖ Nausea, Vomiting & thirst
- ✖ transient visual/ auditory illusions
- ✖ Grand mal seizures (after 7-48 hr alc cessation)

symptoms are possibly due to Rebound **super sensitivity of glutamate** Receptorss & hypoactivity of **GABAergic Receptors.**
-Chronic Intake leads to:Aforementioned symptoms after few hours + After ≥2 days *delirium tremens* maybe due to:

- ✓ **rebound *β-adrenoceptor super-sensitivity***
- ✓ **hyperactivity of neural adaptive mechanism (neuroadaptation) no longer balance by inhibitory effect of alcohol & up regulation of NMDA Receptors**

Management of alcoholism withdrawal

- ✖ Substituting it with *long*-BDZs **(chlordiazepoxide, diazepam)** OR *short* acting are **preferable (lorazepam)**
- ✖ Manage withdrawal symptoms & prevent irritability, insomnia, agitation & seizures.
- ✖ Dose of BDZs should **be carefully adjusted to provide efficacy & avoid excessive** dose that causes **respiratory depression & hypotension.**
- ✖ **Clonidine (α_2 agonist); inhibit** enhanced sympathetic Norepinephrine release.
- ✖ **Propranolol**; inhibit action of exaggerated sympathetic activity
- ✖ **Naltrexone**; po, an opioid antagonist, reduce **psychic craving** for alcohol in abstinent patients & reduce relapse.
- ✖ **Acamprosate**; a weak **NMDA-R** antagonist & **GABA activator**, reduce psychic craving. It is given po for 3- 12 months to alcohol dependent patients to inhibit neuronal excitability.