# #3

# Alcohol and the brain

Revised by prof. Hanan Hagar

## Objectives:

- Recognize the pharmacokinetic aspects of alcohol
- Know the difference between the pharmacological actions of acute (immediate) and chronic alcohol administration.
- Know the complications associated with alcoholism
- Understand the pharmacology of drugs used for treating alcohol addiction and relapse
- Identify the teratogenic effects of alcohol on pregnant women
- Recognize the drug interactions between alcohol and other medications taken concomitantly

## Color index:

- Drugs names
- Doctors notes
- Important
- Extra

We suggest you to have a quick revision of Metabolism of drugs lecture

# Ethyl Alcohol

## Ethyl alcohol (ethanol):

most commonly abused drug in the world.

## Pharmacokinetics

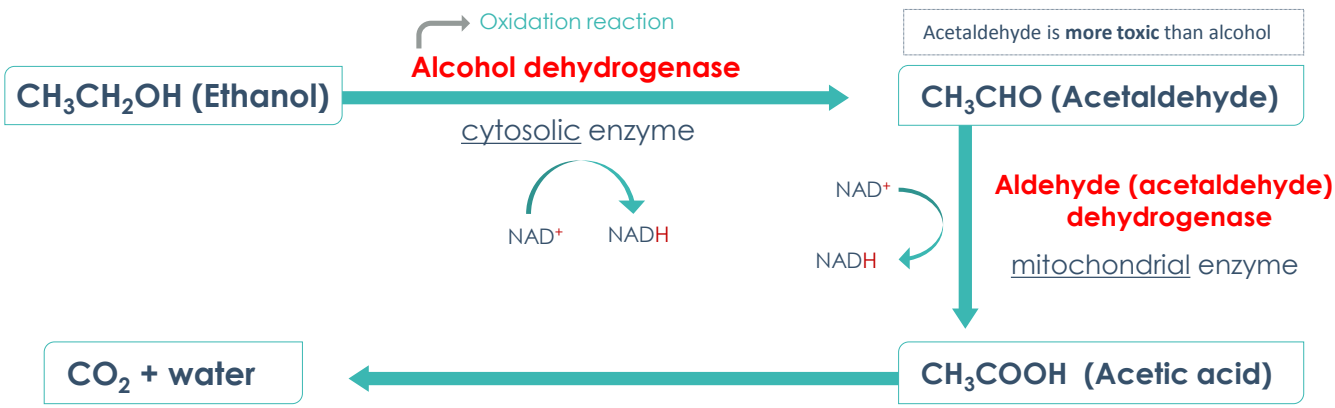
- Small lipophilic molecule → readily crosses all biological membranes.
- Rapidly & completely absorbed from GIT
- Has large Vd (distributed to all body tissues) → **Volume of distribution = Total body water (0.5-0.7 L/kg)**. "multi compartment distribution"
- Crosses **placenta** and excreted in milk.
- **Acute** alcohol consumption inhibits **CYP450 2E1** → ↓ metabolism of other drugs taken concurrently as (**warfarin**, **phenytoin**).
- **Chronic** alcohol consumption induces liver microsomal enzyme **CYP450 2E1**, which leads to significant increases in ethanol metabolism (Tolerance) & metabolism of other drugs as **warfarin** (Drug interactions).

### Metabolism in gastric mucosa & liver

- Oxidation of **ethanol** to **acetaldehyde** via ***alcohol dehydrogenase*** (major) or ***cyt-p450*** (minor) (CYP2E1).
- **Acetaldehyde** is converted to **acetate** via *aldehyde dehydrogenase* which also reduces NAD**+** to NAD**H**.
- **Acetate** ultimately is converted to $CO_2$ + water.
- At **low** ethanol conc. → **minor** metabolism by MEOS (**microsomal ethanol-oxidizing system**) mainly cyt-p450 (CYP2E1).
  → Upon **continuous (chronic)** alcohol use, this enzyme is stimulated and contribute significantly to ↑ **alcohol metabolism & tolerance**. → the microsomal enzymes will take the upper hand in metabolism of alcohol in this case.

## Alcohol metabolism (**major pathway**)

90-98% in **liver**
Depends on cytosolic enzyme (alcohol dehydrogenase)



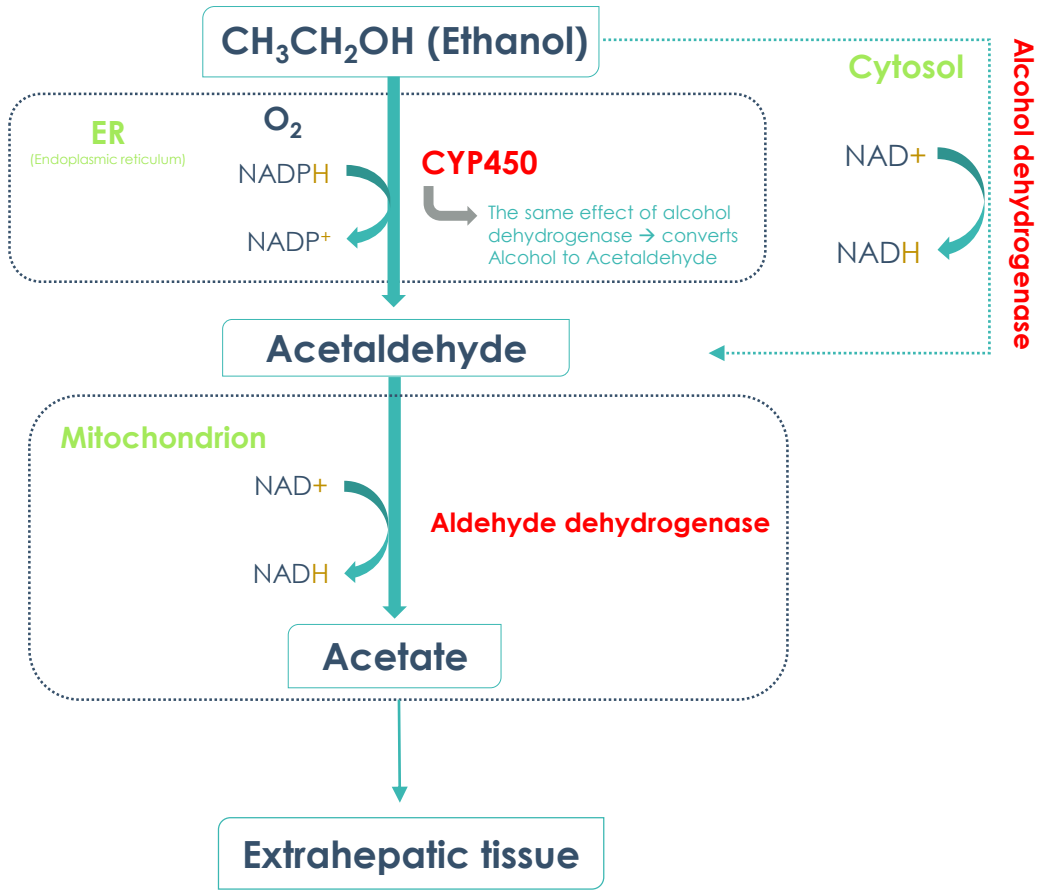

* NAD+/NADH: nicotinamide adenine dinucleotide

# Ethyl Alcohol

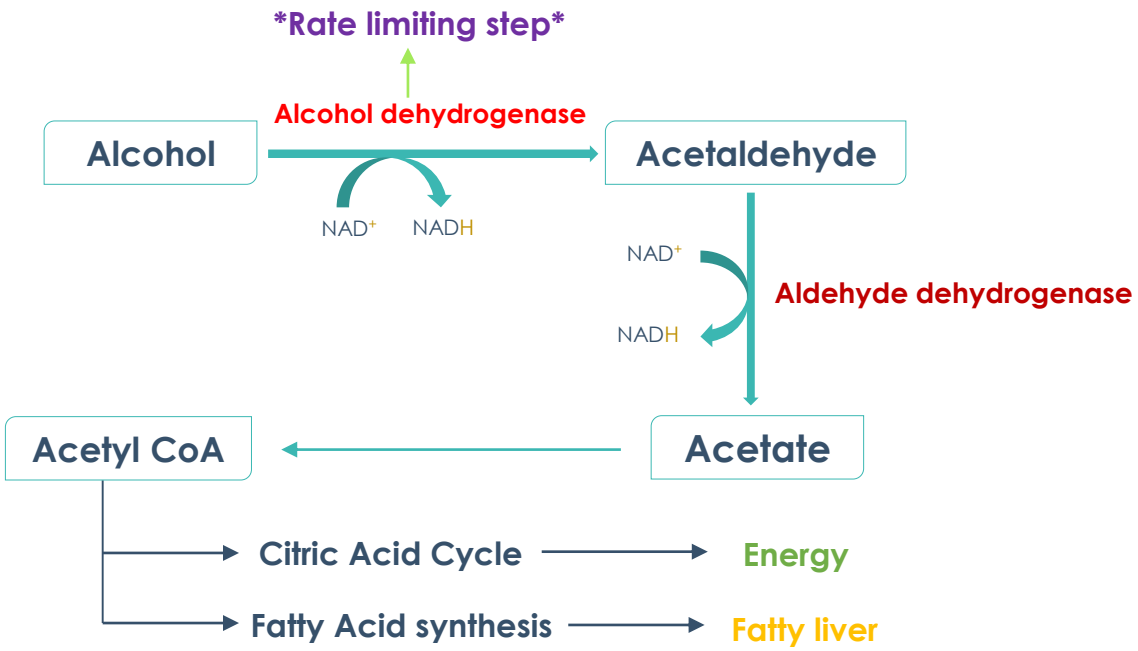
## Hepatic cellular processing of alcohol (**minor pathway**):

Depends on the **microsomal enzymes**

If alcohol is taken in **low conc.** → minor pathway will start its function.
But if it taken for prolonged time, even in low conc. → chronic alcohol abuse → induction of liver enzymes → **tolerance** is developed → upregulation of microsomal enzymes → result in **addiction**. (psychological & physiological symptoms )




## **Hepatic** ethanol metabolism:



# Genetic variation of alcohol metabolism

## Aldehyde Dehydrogenase polymorphism*:

- **Asian** populations (including Chinese, Japanese, Taiwanese, Korean) have genetic variation in **aldehyde dehydrogenase** resulting in a variant allele **ALDH2*2**.

→ Which means that **acetaldehyde** can NOT be converted to acetate due to **aldehyde dehydrogenase deficiency**.
- They metabolized alcohol at **slower** rate than other populations.
- Can develop "**Acute acetaldehyde toxicity**" after alcohol intake characterized by **nausea**, **vomiting**, **dizziness**, **headache**, **vasodilatation**, and **facial flushing** → it has a beneficial effect → This Strongly protect against alcohol-use disorders and prevent them from becoming alcoholic.

*Polymorphism is the existence of one gene in different forms.

**Facial flushing before and after drinking alcohol.**

## Alcohol excretion:

- Excreted unchanged in **urine** (2-8%).
- Excretied unchanged via **lung** (basis for **breath alcohol test**).
- Rate of elimination is **zero-order kinetic** (not conc.-dependent) i.e. rate of elimination is the same at low and high concentration → Any change in its conc. → toxicity.

## Mechanism of action of alcohol:

Alcohol is a CNS **depressant**

| Acute alcohol | Chronic alcohol |
|---|---|
| - **Enhancement the effect of GABA** (inhibitory neurotransmitter) **on its GABA receptors** in brain → CNS depression.<br><br>- **Inhibition of glutamate action** (excitatory neurotransmitter) **on NMDA** (N-methyl-d-aspartate) **receptors** → disruption in memory, consciousness, and alertness. | - **Up-regulation of NMDA receptors** & voltage sensitive $Ca^{2+}$ channels ($Ca^{2+}$ influx to nerve cells).<br>→ Leading to **alcohol tolerance** & **withdrawal symptoms** (tremors, exaggerated response & seizures).<br>- Chronic means **low** doses in **prolonged** time. |

# Acute actions of alcohol
(depends on the **conc.**)

## In mild-moderate amounts

- **CNS depression:**
  - Relieves anxiety, euphoria (feeling of well-being).
  - Nystagmus, slurred speech, impaired judgment, and ataxia.
  - Sedation, hypnosis, loss of consciousness.

- **CVS depression:**
  - Myocardial contractility **depression**
  - Vasodilatation (**flush**) due to vasomotor center depression & direct smooth muscle relaxation caused by **acetaldehyde**. → hypothermia may be marked in sever overdose.

## In severe amounts

- Severe CNS depression
- Respiratory acidosis
- **CVS depression**
- **Hypotension**
- **Respiratory depression.** Most common cause of death.
- Nausea, vomiting, aspiration of vomitus.
- Volume depletion (dehydration)
- Hypothermia → in large doses.
- **Coma**, **death** (if it combined with sleeping pills → CNS depression).

# Chronic actions of alcohol

- **Chronic** ethanol abuse (**alcoholism** = addiction) is associated with many complications:

**Tolerance** | **Dependence** | **Addiction** | **Behavioral changes**

### Liver
hepatic cirrhosis & liver failure.

### CVS
**Hypertension** & myocardial infarction

### Hematology
Hematological disorders & neoplasia.

### GIT
irritation, inflammation, bleeding, nutritional deficiencies

### CNS
cerebral atrophy, cerebellar degeneration, and peripheral neuropathy. Wernicke encephalopathy or Korsakoff psychosis* may occur.

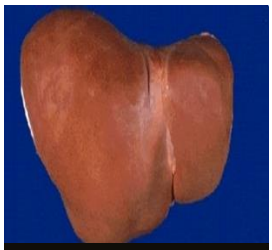
### Endocrine
gynecomastia & testicular atrophy Hematological disorders, neoplasia.

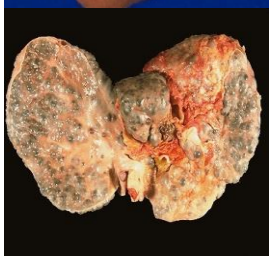
* Korsakoff syndrome is a chronic memory disorder caused by severe deficiency of thiamine (vitamin **B1**)

# Complications Of Chronic Alcohol Use (Alcoholism)

## Liver

**The most common medical complication occurs with liver:**


Healthy Liver


Liver in chronic alcoholics

**1-Reduction of gluconeogenesis**

**2- Fatty liver/ alcoholic steatosis**

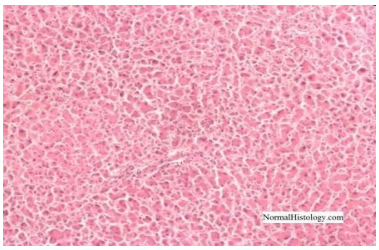
Reduction of gluconeogenesis → accumulation of Acetyl co A
→ energy production from alcohol rather than from fat
→ accumulation of fat → (fatty liver)

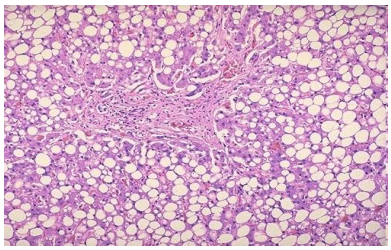
**3-Hepatitis**

**4- Hepatic cirrhosis:**
**jaundice, Ascites, bleeding, encephalopathy.**
(liver metabolism not going properly → accumulation ammonia → enter brain → encephalopathy)

**5- Irreversible liver failure.**
Acetate converted to other product Acetyl co A "other than CO2+ H2O".
In over drinking → depletion of NAD will be in reduced form →
all enzymes depend on NAD will not work → That lead to accumulation of Acetyl co A → converted into fatty acid→ deposition in liver → first step injury happen in liver on drinking alcohol.

**Healthy Liver vs Fatty Liver**



**Acetaldehyde** is more toxic than alcohol → causing inflammation and **fat cell proliferation**

**- Alcoholic Liver Disease:**
Normal Liver ⇄ **Steatosis** (infiltration of liver cells with fat) ⇄ **Steatohepatitis** ( inflammation of the liver with concurrent fat accumulation in liver) ⇄ **Cirrhosis** (a chronic disease of the liver marked by degeneration of cells, inflammation, and fibrous thickening of tissue)

- Fatty liver → inflammation→ hepatitis → fibrosis "liver not functioning" → cirrhosis

## GIT System

- **Gastritis, hemorrhagic esophagitis, ulcer diseases, pancreatitis** (due to direct toxic action on epithelium)

- It injures the **small intestine**, leading to:
  - **Diarrhea** → decrease the absorption in the intestine.
  - **Deficiency of vitamins.**
  - **Exacerbates nutritional deficiencies**
  - **weight loss, and malnutrition** (due to malabsorption)
  - In heavy drinkers: increased risk of **oral** and **esophageal cancer.**

# Complications Of Chronic Alcohol Use (Alcoholism)

## Cardiovascular System

**1- Chronic** alcohol abuse can lead to **cardiomyopathy**
**2- Cardiac hypertrophy, fibrosis.**
**3- Congestive heart failure.**
**4- Arrhythmia** → due to **$K^+$** and **$Mg^{2+}$** depletion as well as enhanced release of catecholamines.
**5- Hypertension** → due to increased **$Ca^{2+}$** & sympathetic activity.
* Alcohol is the most common cause of **reversible hypertension**.

## Hematological complications

**1- Iron deficiency anemia** (due to inadequate dietary intake "low absorption" & GIT bleeding).
**2- Megaloblastic anemia:** (due to **folate deficiency**, malnutrition, impaired folate absorption).
**3- Hemolytic anemia.**
**4- Bone marrow suppression**
**5- Thrombocytopenia** (suppressing platelet formation, prolong bleeding times).
**6- Impaired production of vitamin-K dependent clotting factors** leading to prolonged prothrombin time.

## Endocrine system

**1- Hypogonadism** (reduction or absence of hormone secretion or other physiological activity of the gonads (testes or ovaries)) :

- In **women:** ovarian dysfunction, amenorrhea (n abnormal absence of menstruation) , anovulation, **hyperprolactinemia** (high prolactin) → infertility.

- In **men:** gynecomastia, decreased muscle & bone mass, testicular atrophy, sexual impotence due to inhibition of luteinizing hormone (**LH**), decrease in **testosterone**, estradiol, progesterone.

**2- Hypoglycemia & ketoacidosis** due to impaired **hepatic gluconeogenesis** & excessive lipolytic factors, especially increased **cortisol** and **growth hormone**.

## Central Nervous System

**1- Tolerance**
**2- Physiological and psychological dependence**
Physiological Dependence refers to the process throughout which a body becomes dependent upon a foreign substance,Ex. person becomes addicted to alcohol or drugs.

**3- Addiction: dopamine, serotonin and opioids are involved.**
**4- Neurologic disturbances**
**5- Wernicke-Korsakoff syndrome**
Vitamins deficiency→ A,D,B"B1"→ Wernicke encephalopathy or Korsakoff psychosis may occur.

# Chronic Alcoholism Associated Syndromes

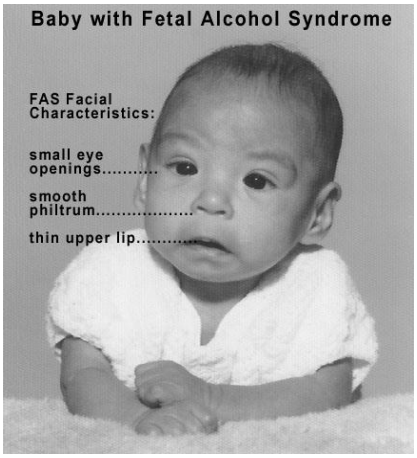
## Fetal Alcohol Syndrome (FAS): Irreversible

- Alcohol is the leading cause of mental retardation and congenital malformation.
- Ethanol rapidly crosses placenta → the fetal liver has little or no **alcohol dehydrogenase** → fetus must rely on maternal & placental enzymes for elimination.

**Pre-natal** exposure to alcohol causes:

1. **Intrauterine growth retardation (due to hypoxia)**
2. **Congenital malformation (teratogenesis):**

a. Microcephaly
b. Impaired facial development
c. Congenital heart defects
d. Physical and mental retardation.




## Wernicke-Korsakoff syndrome

**It is a combined manifestation of 2 disorders:**

**- Wernicke's encephalopathy:**
characterized by:
1. ocular disturbances.
2. unsteady gait.
3. changes in mental state as confusion, delirium(هذيان), ataxia.

**- Korsakoff's psychosis:**
1. Impaired memory
2. Cognitive and behavioral dysfunction.

**Cause:** Thiamine (**vit. B1**) deficiency (rarely seen with absence of alcoholism)
**Due to**: inadequate nutritional intake, ↓uptake of thiamine from GIT & ↓liver thiamine stores.

**Treated by:** **Thiamine + dextrose-containing IV fluids**

## Alcoholism Tolerance

**Chronic** consumption of alcohol leads to tolerance.
develops due to:

**- Metabolic tolerance** (pharmacokinetic):
→ Change in the absorption, distribution, metabolism, excretion.
due to induction of **liver microsomal enzymes** (e.g. CYP450).

**- Functional tolerance** (Pharmacodynamic):
→ Change in the receptors.
due to **change in CNS sensitivity**.

## Alcoholism withdrawal symptoms:

There symptoms result from high sympathetic activity & upregulation of the receptors

- Autonomic hyperactivity & craving for alcohol
- Vomiting, thirst
- Profuse sweating, severe tachycardia
- Vasodilatation, fever
- Delirium(هذيان), tremors, anxiety, agitation, insomnia
- Transient visual/ auditory illusions, violent behavior, hallucinations.
- Grand mal **seizures** (after 7-48 hr alcohol cessation)

  Due to super-sensitivity of **glutamate receptors** & Hypo-activity of **GABA receptors** are possibly involved.

## Management of alcoholism withdrawal:

The Management of alcoholism withdrawal is substituting alcohol with a long-acting sedative hypnotic drug then tapering the dose.

**Management of Alcoholism Withdrawal**

- **Benzodiazepines**
  - as (**chlordiazepoxide**, **diazepam**) → long acting drug.

    Or **lorazepam** that is **preferable** (**shorter** duration of action)
  - should be carefully adjusted to provide **efficacy** (via **IV/po**) & Manage withdrawal symptoms & prevent irritability, insomnia, agitation & seizures.

    Avoid excessive dose that causes **respiratory depression** & **hypotension**
- **Fluoxetine**
  (Serotonin reuptake inhibitors)
- **Clonidine**
  **Propranolol**
  (nonselective beta-blocker)
  - **Clonidine** is $a_2$ agonist **presynaptic**

    **inhibits** the action of exaggerated **sympathetic** activity
- **Acamprosate**
  - weak **NMDA receptor antagonist** & **GABA activator** → reduce **psychic craving** (reduce risk of relapse)

## To prevent alcohol relapse:

**Disulfiram** therapy: 250 mg **daily** → **Inhibits hepatic aldehyde dehydrogenase** → increase blood level of **acetaldehyde** → **Disulfiram**-induced symptoms render alcoholics afraid from drinking alcohol → **Acetaldehyde** produces extreme **discomfort**, **vomiting**, **diarrhea**, **flushing**, **hotness**, **cyanosis**, **tachycardia**, **dyspnea**, **palpitations** & **headache**

# Alcohol and drug interactions

**Acute alcohol use** (large dose):

causes **inhibition of liver enzyme**, → **decreases metabolism** of some drugs and **increases their toxicities** e.g. **bleeding** with **warfarin**

**Chronic alcohol use** (continuous use):

**induces liver microsomal enzymes** → **increases metabolism** of drugs such as **warfarin**, **propranolol**

1. **Acetaminophen** + alcohol (chronic use)= risk of **hepatotoxicity**. → due to increased production of free radical metabolite of acetaminophen
   → High metabolism of high doses of acetaminophen (بيأخذ كمية أكبر من الشخص العادي عشان يعطيه التأثير) → high free radicals (result from metabolism by microsomal enzymes) → hepatotoxicity
2. NSAIDs + alcohol = Increase in the risk of developing a **major GI bleed** or an **ulcer**.
   Bc NSAIDs may causes ulcer and bleeding, so the combination increases the risk of ulcer & bleeding
3. Narcotic drugs (**codeine** and **methadone** → CNS depression drugs) + alcohol = risk of **respiratory** and **CNS depression**

* Alcoholic pts = chronic use

Alcohol **suppresses gluconeogenesis**, which may increase risk for **hypoglycemia** in **diabetic patients**.

# Summary of Alcoholism-1

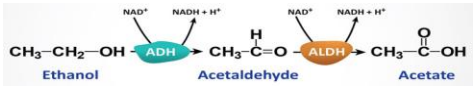
## Pharmacokinetics

- Small lipophilic molecule.
- Crosses all biological membranes.
- Large Vd (distributed to all body tissues)
- Volume distribution = Total body water.
- Crosses placenta and excreted in milk.
- Rapidly & completely absorbed from GIT.

- Acute alcohol consumption inhibits CYP450 2E1 so decrease metabolism of other drugs taken concurrently as (warfarin, phenytoin).
- Chronic alcohol consumption induces liver microsomal enzyme CYP450 2E1, leads to Tolerance & Drug interactions (e.g. warfarin)

## Alcohol Metabolism

**Metabolism in gastric mucosa & liver (90-98% in the liver).**




- Acetate ultimately is converted to $CO_2$ + water.
- **At low ethanol conc.**, minor metabolism by MEOS (microsomal ethanol-oxidizing system) mainly cyt-p450 (CYP2E1). Upon continuous alcohol use, this enzyme is stimulated and contribute significantly to **alcohol metabolism & tolerance.**

**Genetic variation of alcohol metabolism**

**Aldehyde Dehydrogenase polymorphism**

- Asian populations have genetic variation in aldehyde dehydrogenase resulting in a variant allele ALDH2*2 (They metabolize alcohol at slower rate)
- Can develop **"Acute acetaldehyde toxicity"**

## Alcohol excretion

- Excreted unchanged in urine (2-8%).
- Excretion unchanged via lung (basis for breath alcohol test).
- Rate of elimination is zero-order kinetic (not concentration-dependent)

## Mechanism of action

### CNS depressants

**Acute alcohol** causes:

- **Enhancement the effect of GABA.**
- **Inhibition of glutamate action.**

**Chronic alcohol** causes:
**up-regulation of** NMDA receptors & voltage sensitive Ca channels, leading to alcohol tolerance & withdrawal symptoms.

# Alcoholism Associated Syndromes

## Fetal Alcohol Syndrome (FAS): Irreversible

Ethanol rapidly crosses placenta
Pre-natal exposure to alcohol causes:

- Intrauterine growth retardation
- Congenital malformation (**teratogenesis**):
  - Microcephaly
  - Impaired facial development
  - Congenital heart defects
  - Physical and mental retardation.

## Wernicke-Korsakoff syndrome

It is a combined manifestation of 2 disorders:

**Wernicke's encephalopathy**: characterized by ocular disturbances, unsteady gait changes in mental state (confusion, delirium, ataxia)

**Korsakoff's psychosis:** impaired memory & cognitive and behavioral dysfunction.

**Cause: thiamine (vitamin B1) deficiency**
**Treated by: thiamine** + **dextrose**-containing IV fluids.

# Summary of Alcoholism-2

## Acute actions of alcohol

**CNS depression**

- relieves anxiety, euphoria.
- Nystagmus, slurred speech, impaired judgment, ataxia.
- Sedation, hypnosis, loss of consciousness

**CVS depression**

- Myocardial contractility depression
- Vasodilatation due to vasomotor center depression & direct smooth muscle relaxation caused by acetaldehyde.

**In severe amounts**

Severe CNS depression, respiratory acidosis & depression, Nausea, vomiting, aspiration of vomitus, CVS depression, Volume depletion, Hypotension, Hypothermia, Coma, death.

## Chronic actions of alcohol

- **Tolerance, dependence, addiction, behavioral changes.**
- **Liver**: hepatic cirrhosis & liver failure.
- **CVS:** hypertension, myocardial infarction
- **CNS:** cerebral atrophy, cerebellar degeneration, and peripheral neuropathy. Wernicke encephalopathy or Korsakoff psychosis may occur.
- **GIT system:** irritation, inflammation, bleeding, nutritional deficiencies
- **Endocrine system:** gynecomastia & testicular atrophy
- Hematological disorders, neoplasia.
- **Liver** (The most common medical complication)
  - Reduction of gluconeogenesis
  - Fatty liver/ alcoholic steatosis
  - Hepatitis
  - **Hepatic cirrhosis**: jaundice, ascites, bleeding, encephalopathy.
  - Irreversible liver failure.

## Alcoholism Complications

**GIT**

- Exacerbates nutritional deficiencies.
- weight loss, and malnutrition.
- In heavy drinkers : increased risk of oral and esophageal cancer.
- Gastritis, hemorrhagic esopahgitis, ulcer, pancreatitis.
- Diarrhea.
- Deficiency of vitamins.

**CVS**

Can lead to **cardiomyopathy**, Cardiac hypertrophy, CHF, **Arrhythmia, Hypertension**.

**Hematological complications**

- **Iron deficiency anemia**
- **Megaloblastic anemia**.
- **Hemolytic anemia**.
- **Bone marrow suppression**
- **Thrombocytopenia**.
- Impaired production of **vitamin-K dependent clotting factors.**

**Endocrine system**

**Hypogonadism:**

- **In women:** ovarian dysfunction, amenorrhea, anovulation, hyperprolactinemia, infertility.
- **In men:** gynecomastia, decreased muscle & bone mass, testicular atrophy, sexual impotence due to inhibition of luteinizing hormone (LH) , decrease in testosterone, estradiol, progesterone.

**Hypoglycemia & ketoacidosis** due to impaired hepatic gluconeogenesis & excessive lipolytic factors, especially increased cortisol and growth hormone.

**CNS**

- Tolerance
- Neurologic disturbances
- **Wernicke-Korsakoff syndrome**
- Physiological and psychological dependence
- Addiction: **dopamine, serotonin and opioids** are involved.

# Summary of Alcoholism-3

## withdrawal symptoms

- Autonomic hyperactivity & craving for alcohol.
- Vomiting, thirst.
- Profuse sweating, severe tachycardia
- Vasodilatation, fever
- Delirium, tremors, anxiety, agitation, insomnia
- transient visual/ auditory illusions, violent behavior, hallucinations.
- Grand mal **seizures**

Due to super-sensitivity of glutamate receptors & hypoactivity of GABA receptors are possibly involved.

## Alcoholism Tolerance

**- Metabolic tolerance (**pharmaco**kinetic):** due to induction of liver microsomal enzymes.

**- Functional tolerance (**Pharmaco**dynamic):** due to change in CNS sensitivity.

## Management of withdrawal

- Substituting alcohol with a long-acting sedative hypnotic drug then tapering the dose.
- **Benzodiazepines** as (**chlordiazepoxide, diazepam**) or **lorazepam** that is preferable (shorter duration of action).
- **Efficacy:** IV/ PO
- 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.
- **Fluoxetine**
- **Clonidine & Propranolol**: inhibits the action of exaggerated sympathetic activity
- **Acamprosate:** a weak NMDA receptor antagonist & GABA activator, reduce psychic craving.

## To prevent alcohol relapse:

**Disulfiram therapy**: 250 mg daily
Inhibits hepatic **aldehyde dehydrogenase**, this will increase blood level of **acetaldehyde.**
Disulfiram-induced symptoms render alcoholics afraid from drinking alcohol.
Acetaldehyde produces extreme discomfort, vomiting, diarrhea, flushing, hotness, cyanosis, tachycardia, dyspnea, palpitations & headache.

## Alcohol and drug interactions

| **Acute alcohol use** | **Chronic alcohol use** | **Other** |
|---|---|---|
| Inhibition of liver enzyme, decreases metabolism of some drugs and increases their toxicities e.g. **bleeding** with **warfarin** | Induces liver microsomal enzymes and increases metabolism of drugs such as **warfarin, propranolol** and etc. | Alcohol suppresses **gluconeogenesis,** which may increase risk for hypoglycemia in diabetic patients.<br>**Acetaminophen + alcohol** (chronic use)**:** risk of hepatotoxicity.<br>**NSAIDs + alcohol:** Increase in the risk of developing a major GI bleed or an ulcer.<br>**Narcotic drugs (codeine and methadone) + alcohol**: risk of respiratory and CNS depression. |

Flash Cards | MCQs | Editing File

# Thank you for checking our team!

Pharmacology 435

@ pharmacology435

**أثير النشوان**

أسرار باطرفي
العنود العمير
آية غانم
حصه المزيني
دلال الحزيمي
رغدة قاسم
ريم العقيل
سارا الحسين
ساره الخليفة
لمى الزامل
لولوه الصغيّر
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قصي عجلان
ماجد العسبلي
محمد ابونيان
محمد السحيباني
يوسف الصامل

Sources:

1- 434's lecture and notes.
2- Wikipedia
3- Pharmacology (Lippincotts Illustrated Reviews Series), 5th edition
4- Basic & Clinical Pharmacology by Katzung. Chapter 23, 12th edition


Revised by
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