MED437
KING SAUD UNIVERSITY

Pharmacology
435 team

Pharmacology
Team 437

# Alcohol and the brain

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Editing File

# Ethyl Alcohol

Medically it's only used topically as antiseptic drug

## 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 (volume of distribution) (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).here patient might have bleeding if use warfarin
- **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). here patient might have DVT(deep vein thrombosis)

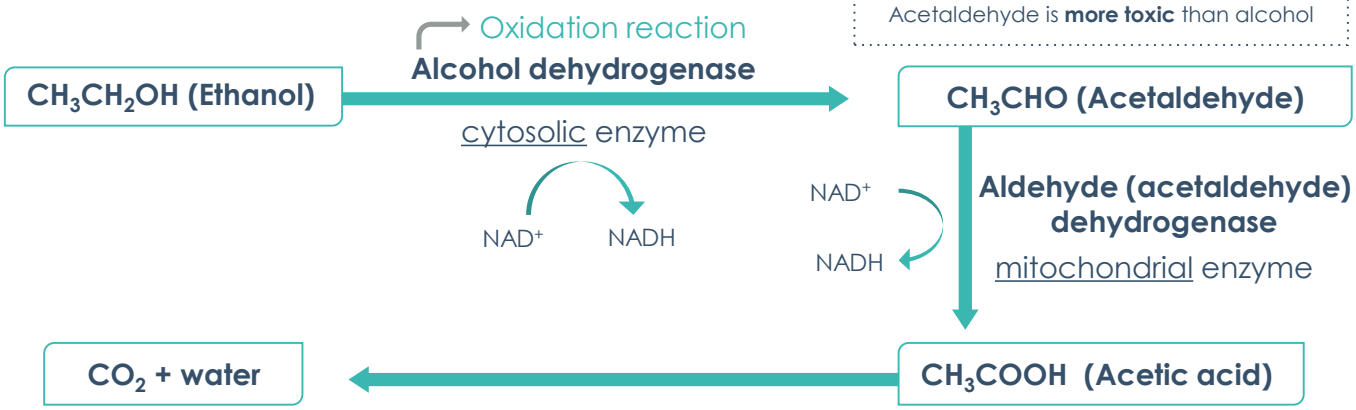
### Metabolism in gastric mucosa & liver

- Oxidation of **ethanol** to **acetaldehyde** via alcohol dehydrogenase or **cyt-p450** (CYP2E1).
- **Acetaldehyde** is converted to **acetate** via aldehyde dehydrogenase which also reduces NAD**+** to NAD**H**. (Co-factor)
- **Acetate** ultimately is converted to $CO_2$ + water (to decrase the oxdtive stress)
- 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**.

## Alcohol metabolism (major pathway)

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

Acetaldehyde is **more toxic** than alcohol



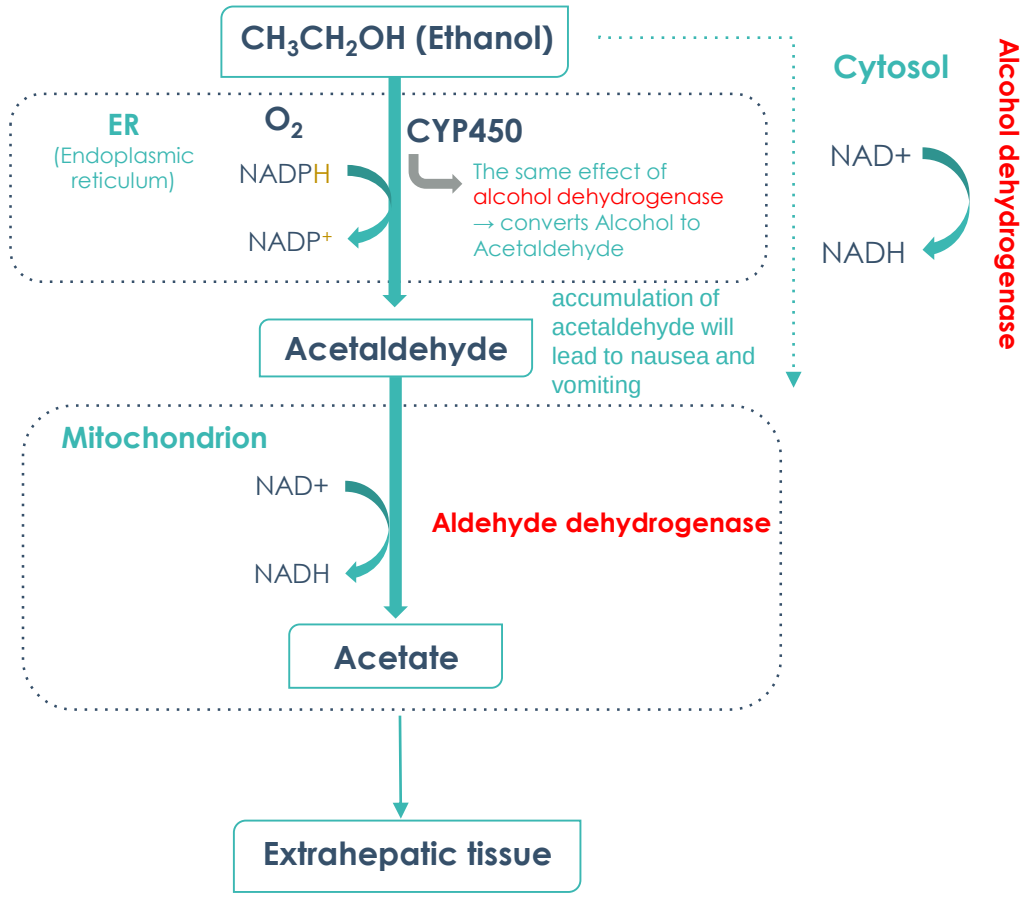

* NAD+/NADH: nicotinamide adenine dinucleotide

# Ethyl Alcohol

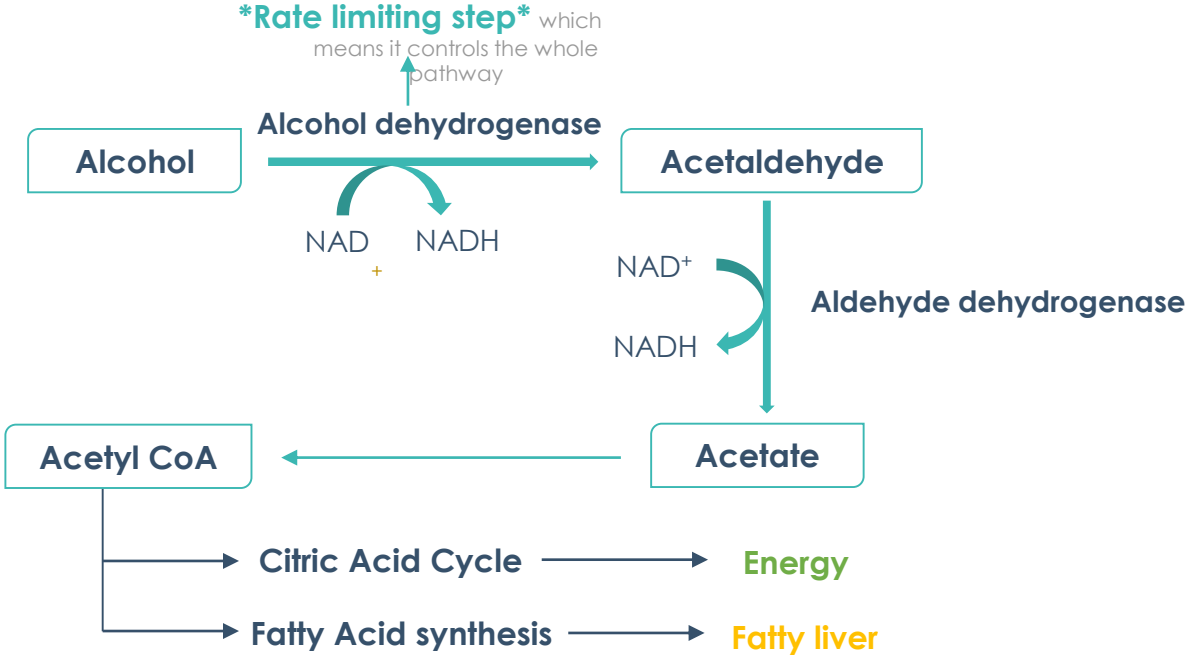
## Hepatic cellular processing of alcohol (minor pathway):

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 → 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.

## Alcohol excretion:

- Excreted unchanged in **urine** (2-8%).
- Excreted 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 (increase) 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>- **Inhibition of glutamate action** (excitatory neurotransmitter) **on NMDA** (N-methyl-d-aspartate) **receptors** → disruption in memory, consciousness, and alertness.<br>that's why it's contraindicated for drivers | **Up-regulation of NMDA receptors** & voltage sensitive $Ca^{2+}$ channels ($Ca^{2+}$ influx to nerve cells).1<br>→ Leading to **alcohol tolerance** & **withdrawal symptoms** (tremors, exaggerated response & seizures).1<br>- Chronic means **low** doses in **prolonged** time<br>GABA will be down-regulated. |

باختصار الفرق بين الاكيوت و الكرونك .ان الاكيوت للحين ما صار فيه تغيير بتركيب الريسيبتورز لمن يبدا الشخص يستخدم الكحول يصير فيه بلوك للقلوتاميت ريسيبتورز فيبدأ الجسم يحس انه فيه شي غلط فيزيد عدد الريسيبتورز حقت القلوتاميت علشان كذا لمن المدمن يوقف استخدام الكحول يكون عنده قلوتاميت ريسيبتورز كثير ولمن يرجع عمل القلوتاميت طبيعي يصير عندنا اوفر ستيميوليشن للقلوتاميت ريسيبتورز )لانها صارت كثيره (علشان كذا تطلع عنده اعراض ترك الكحول الميكانزم هذا كله اسمه (Up Regulation)

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

## In mild-moderate amounts

Gradual CNS depressing

### 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 due to : vasomotor center depression & direct smooth muscle relaxation caused by **acetaldehyde**. → hypothermia may be marked in sever overdose

that is why we see redness on their checks

## In severe amounts

| | |
|---|---|
| Severe CNS depression | **Respiratory depression.** Most common cause of death |
| Respiratory acidosis | Nausea, vomiting, aspiration of vomitus |
| **CVS depression** | Volume depletion (dehydration |
| **Hypotension** | Hypothermia → in large doses. |

# Chronic actions of alcohol

T-DAB <o/

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

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

### Liver

hepatic cirrhosis & liver failure. caused by (RAAS)renin-angiotensin-aldosterone

### CVS

**Hypertension** & myocardial infarction & damage blood vessels

### 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:**

**1-Reduction of gluconeogenesis** (decrease glucose conc.)

**2- Fatty liver/ alcoholic steatosis**

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

**3-Hepatitis**

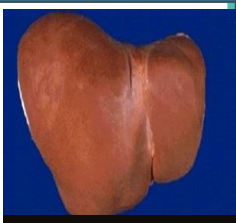
**4- Hepatic cirrhosis:**

**jaundice, Ascites, bleeding, encephalopathy.**

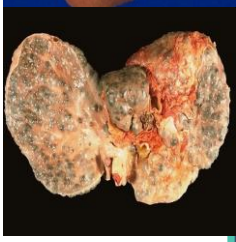
(liver metabolism not going properly → accumulation ammonia → enter brain → encephalopathy)

**5- Irreversible liver failure.**

Acetate converted to other product Acetyl CoA "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 CoA → converted into fatty acid→ deposition in liver → first step injury happen in liver on drinking alcohol.

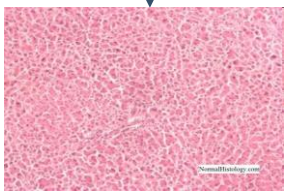


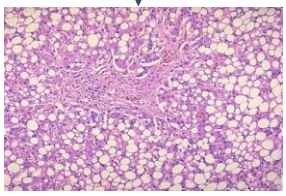
Healthy Liver



Liver in chronic alcoholics

**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)

**mnemonics!!**
**H**assan **G**ave his **U**ncle a **P**ie

- 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).(microcytic anemia)
**2- Megaloblastic anemia:** (due to **folate deficiency**, malnutrition, impaired folate absorption).because of damage to gastric mucosa
**3- Hemolytic anemia.** because of oxidative stress
**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 (in abnormal absence of menstruation) , anovulation, **hyperprolactinemia** (high prolactin) → infertility.

- In **men:** gynecomastia(التثدي), decreased muscle & bone mass, testicular atrophy, sexual impotence due to inhibition of luteinizing hormone (**LH**), decrease in **testosterone**, estradiol, progesterone.
in short term it increase sexual ability
in long term (months or years)it cause impotence

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

## Central Nervous System

**1- Tolerance** due to Up regulation
**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**(major transmitter for drug addiction), **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.

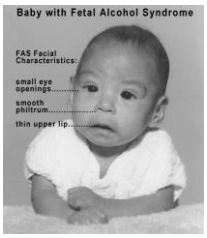
# Chronic Alcoholism Associated Syndromes

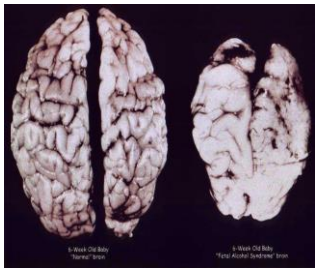
## Fetal Alcohol Syndrome (FAS): Irreversible

- 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.
- Ethanol rapidly crosses placenta because it is highly lipid soluble and it is very small molecule
- **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.



The right brain is an infant's brain that had pre-natal exposure to alcohol.

## 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.
4. Nystagmus (All these symptoms is caused due to thalamus & hypothalamus damage)

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

**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)1

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

Mnemonic for Alcohol withdrawal **(PAST NITE):**

**P**sychomotor agitation
**A**nxiety
**S**eizures
**T**ransient hallucinations
**N**ausea
**I**nsomnia
**T**remors
**E**xcitability

-for treatment : we give them GABA agonist or glutamate antagonist
-major cause of withdrawal symptoms is high glutamate and low GABA

## 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**
increase GABA

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**
it's increase serotonin level and decrease dopamine
(Serotonin reuptake inhibitors)

**Clonidine Propranolol**
(nonselective beta-blocker)

**Clonidine** is $a_2$ agonist **presynaptic**
**inhibits** the action of exaggerated **sympathetic** activity

**Acamprosate**
بديل للكحول ولا يسبب الإدمان وله نفس **effect**

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**.

# Questions

## MCQs

**1- Which of the following is true about ethanol:**

A. Lipophilic
B. Rapidly & completely absorbed from GIT
C. Cross placenta
D. All above

**2- The deposition of ethanol is:**

A. One-compartment
B. Two-compartment
C. Multi-compartment
D. None of these

**3- Metabolism of ethanol mainly in:**

A. Gastric mucosa
B. Liver
C. Small intestine
D. Large intestine

**4- Which of the following is correct about acute alcohol use with warfarin ?**

A. it decreases its metabolism and may cause thrombosis
B. it increases its metabolism and may cause thrombosis
C. it decreases its metabolism and may cause bleeding
D. it increases its metabolism and may cause bleeding

**5- Acetate ultimately is converted to:**

A. $CO_2$ + water.
B. COOH + ester
C. $O_2$ + water
D. None of these

MCQs Answers:
1- D
2- C
3- B
4- C
5- A

# Questions

## MCQs

**6- Which of the following is cytosolic enzyme:**

A. Alcohol dehydrogenase
B. aldehyde dehydrogenase
C. A & B
D. None of these

**7- Which of the following is mitochondrial enzyme:**

A. Aldehyde dehydrogenase
B. Alcohol dehydrogenase
C. A & B
D. None of these

**8- Which of the following is a side effect of chronic alcoholism ?**

A. Wernicke-Korsakoff syndrome
B. constipation
C. hyperglycemia
D. all

MCQs Answers:
6- A
7- A
8- A

## SAQ

**what is the major site of metabolism of ethanol ?**

-metabolized mainly in the liver.

**how is it metabolized (enzymes and products of ethanol metabolism) ?**

-it gets converted by CYP2E1 into acetaldehyde and by acetaldehyde dehydrogenase
to acetate

**what are the routes of excretion of ethanol and its rate of elimination ?**

- Excreted unchanged in urine - Excretion unchanged via lung
- zero-order kinetic (not concentration-dependent)

**why does the chronic effect of ethanol differ from its acute action ?**

due to tolerance :

- Metabolic tolerance due to induction of liver microsomal enzymes
- Functional tolerance due to change in CNS sensitivity

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**References:**


- Doctors' slides and notes.
- pharmacology Team 435.


Special thank for team 435 ❤

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