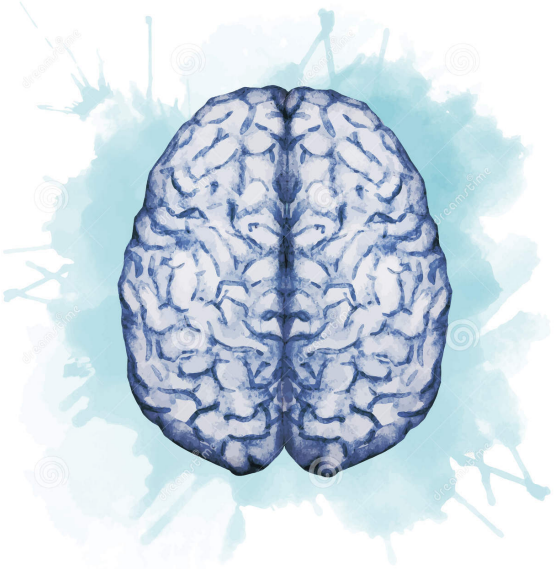
MEDICINE
KING SAUD UNIVERSITY

436 team
pharmacology



Alcohol and the brain

Objectives:

- Describe the pharmacological actions of alcohol
- Describe the pharmacokinetic profile of alcohol
- Describe the development of intoxication symptoms of alcohol
- Describe how alcohol affects various neurotransmitters in the brain.
- Identify various toxicity of alcohols at different organs level
- Describe the addictive nature of alcohol and its mechanism
- Identify alcohol withdrawal symptoms and their management.
- Identify clinically relevant drug interactions with alcohol
- Hazards of alcohol in pregnancy

Color index:

- extra information and further explanation
- important
- doctors notes
- Drugs names
- Mnemonics

تمت المراجعة
شوق الأحمري & عبدالعزيز العنقري

Check out the mnemonics file :
https://docs.google.com/presentation/d/1Z0Vf9oEOJSXo4JIA0mTCk5jB-OU9LP5TFCwz8iBgNac/edit?usp=sharing

Kindly check the editing file before studying this document
https://docs.google.com/presentation/d/1_-g1vol4eBWPet5xVCkuTGFvvnhFF3PJmU0tWtEEw_o/edit?usp=sharing

Ethyl Alcohol (ethanol)

It is the most commonly abused drug in the world

Pharmacokinetics

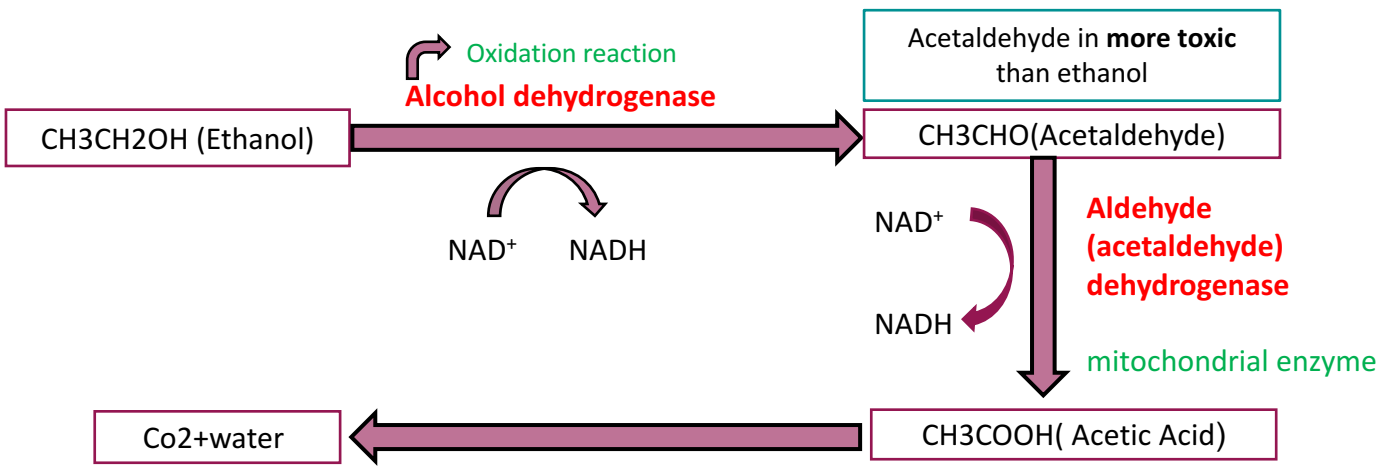
- Small lipophilic (lipid soluble) molecule→ readily crosses all biological membranes.
- Rapidly & completely absorbed from GIT.
- Has high volume of distribution (distributed to all body tissues). →Volume of distribution = Total body water (0.5-0.7 L/kg). "multi compartment distribution" **(plasma + ESF + ICF)**
- Crosses placenta (can easily reach the fetus) and excreted in milk.

Metabolism (in gastric mucosa and liver)

- Oxidation of **ethanol** to ***acetaldehyde*** via **alcohol dehydrogenase (major)** or 2-**CYT-p450 (minor)(CYP-2E1)**.
- Oxidation of Acetaldehyde is converted to **acetate via aldehyde dehydrogenase.** which also reduces NAD+ to NADH.
- **Acetate** ultimately is converted to CO2 + water.
- **At low ethanol concentration** → **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.
- Acute alcohol consumption inhibits **CYP450 especially 2E1** (liver enzyme)→ ↓ 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).
- The microsomal enzymes will take the upper hand in metabolism of alcohol in this case.

Alcohol metabolism (**major** pathway)

Alcohol Metabolism; 90-98% metabolized in liver Depends on cytosolic enzyme (alcohol dehydrogenase)



Hepatic cellular processing of (**minor** pathway)

Depends on the microsomal enzymes

CH3CH2OH (ethanol)

ER (Endoplasmic Reticulum)

O_2

NADPH

NADP+

CYP450

The same effect of alcohol dehydrogenase, Convert alcohol acetaldehyde

cytosol

NAD+

NADH

Alcohol dehydrogenase

Acetaldehyde

*If NAD+ is low in the body, the body will be destroyed by the huge amount of free radicals.

Mitochondrion

NAD+*

NADH

Aldehyde dehydrogenase

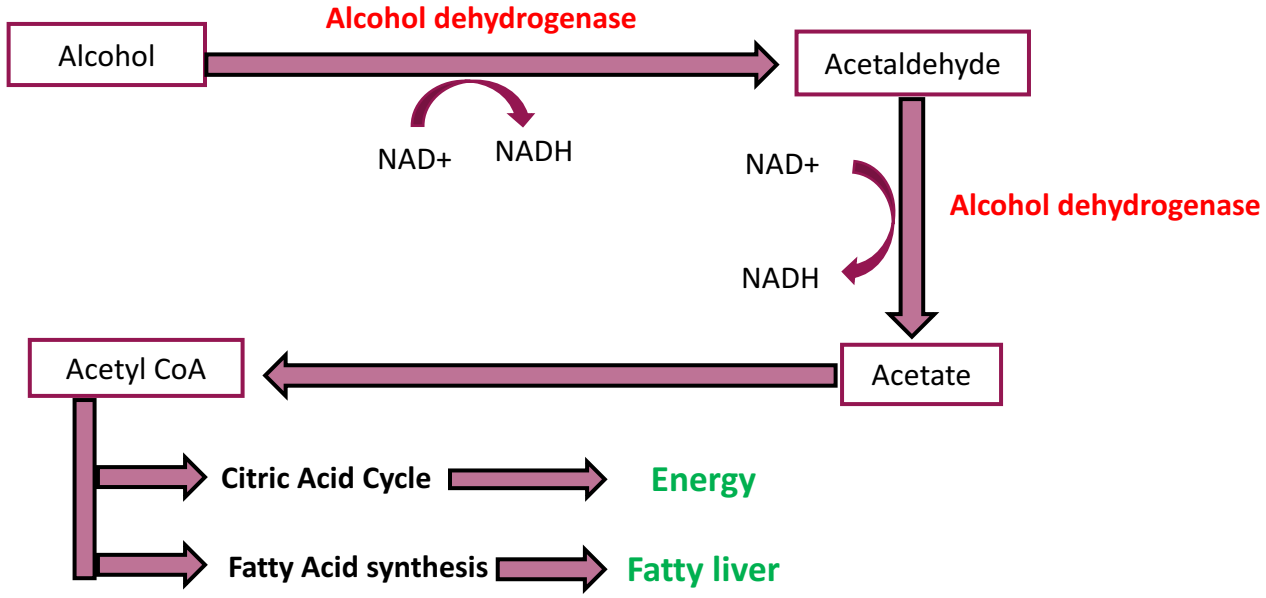
Acetate

Extrahepatic tissue

Low conc. alcohol intake → Minor pathway start function

Prolonged alcohol intake (even if low conc.) → Chronic alcohol abuse → Induction of liver enzymes → Tolerance is developed → Up regulation of microsomal enzymes → Addiction (psychological and 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**.

Genetic variation of alcohol metabolism →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 →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.

Acute acetaldehyde toxicity after alcohol intake characterized by:

Nausea	Vomiting
Dizziness	Vasodilation
Headache	Facial flushing

Explanation : The Asian people will have accumulation of acetaldehyde
So when they get another drink of alcohol more acetaldehyde will be formed so the following characters will start to appear (nausea , vomiting, …) .
And that's one way to treat alcoholism people to let them stop drinking (will be discussed later)

Alcohol (Ethyl alcohol *ethanol*)

Excretion

- Excreted *unchanged* in urine (2-8%).
- Excreted unchanged via lungs (**basis for breath alcohol test**). **(used as driving test)**
- Rate of elimination is zero-order kinetic (*not concentration-dependent*) i.e. rate of (amount of) elimination is the same at low and high concentration.

Mechanism of action

Acute alcohol

- CNS depressant.
  1. **Enhancement the effect of GABA (inhibitory Neurotransmitter)** causing CNS depression.
  2. **Inhibition of glutamate action (excitatory Neurotransmitter)** causing disruption in memory, consciousness and alertness.

Chronic alcohol

- **Up-regulation* of NMDA receptors** and voltage sensitive Ca channels leading to **alcohol tolerance** and **withdrawal symptoms** includes tremor, exaggerated response and seizures. Chronic means low doses in prolonged time.

*↑ NMDA receptors amount →they become more sensitive →begin to be tolerance and if the drinker didn't ↑ the dose →withdrawal symptoms will start to appear

Acute actions of Alcohol

Mild to moderate amount

❖ **On CNS:**

- Relieves anxiety and euphoria(feeling of well-being).
- In higher doses: Nystagmus, slurred speech, impaired judgment and ataxia.
- A little bit higher dose: Sedation, hypnosis and loss of consciousness.

❖ **On CVS:**

- Myocardial contractility depression.
- Vasodilatation due to:
  1. Vasomotor center depression.
  2. Direct smooth muscle relaxation caused by Acetaldehyde.

Sever amounts

- Severe CNS depression.
- Nausea, vomiting and aspiration of vomitus.
- Respiratory depression and acidosis.
- CVS depression.
- Volume depletion.
- Hypotension.
- Hypothermia.
- coma and death.

Chronic actions of alcohol

- Tolerance, dependence, addiction and behavioral changes.
- **Liver:** Hepatic cirrhosis and liver failure.
- **CVS:** hypertension(regarding epithelial cells damage), myocardial infarction.
- **CNS:** cerebral degeneration, and peripheral neuropathy. Wernicke encephalopathy or Korsakoff psychosis may occur. (explained later in slide 8)
- **GIT:** irritation, inflammation, bleeding and nutritional deficiencies.
- **Endocrine system:** gynecomastia (Enlarged breasts in men) and testicular atrophy.
- **hematology**: hematological disorders, neoplasia.

Complications Of Chronic Alcohol Use (Alcoholism)

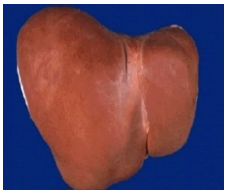
Organ/ system	Complications

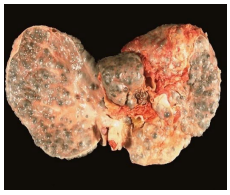
Liver

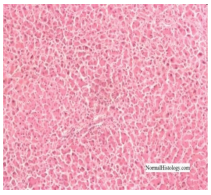
❖ **The most common complications includes:**

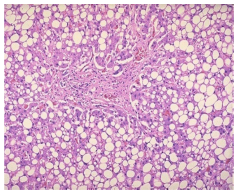
1. Reduction in gluconeogenesis. → Hypoglacemia
2. Alcoholic Fatty liver/ Alcohol steatosis. Reduction of gluconeogenesis →accumulation of Acetyl co A →energy production from alcohol rather than from fat →accumulation of fat →(fatty liver)
3. Hepatitis. **jaundice, Ascites, bleeding, encephalopathy**.(liver metabolism not going properly →accumulation ammonia → enter brain →encephalopathy)
4. Hepatic cirrhosis: jaundice, ascites, bleeding and 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.

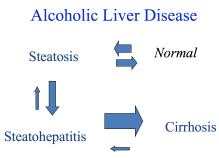
❖ Hypoglycemia and ketoacidosis due to impaired hepatic gluconeogenesis and excessive lipolytic factors especially increased cortisol and growth hormone.


Healthy liver


Liver in chronic alcoholics


Normal liver


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

❖ **Gastritis, hemorrhagic esophagitis, ulcer diseases and pancreatitis** due to direct toxic action on epithelium.

❖ **Diarrhea.**.

❖ **Deficiency of vitamins.** →decrease the absorption in the intestine →due to diarrhea

❖ **Exacerbates nutritional deficiencies.**

❖ **Weight loss and malnutrition.** (due to malabsorption)

❖ **In heavy drinkers: increased risk of oral and esophageal cancer**

CVS

❖ Chronic alcohol abuse can lead to cardiomyopathy including:

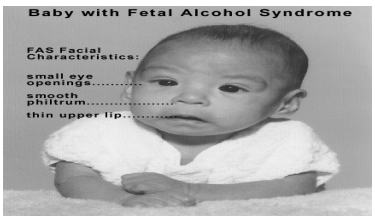
1. **Cardiac hypertrophy.**
2. **Congestive heart failure.**
3. **Arrhythmias** due to K^+ and Mg^{2+} depletion as well as enhanced release of catecholamine.
4. **Hypertension** due to increased calcium and sympathetic activity also by producing substances that attack the vascular epithelial cells.
   - Alcohol is the most common cause of reversible hypertension.

<table>
<tr><th>Organ/ system</th><th colspan="3">Complications</th></tr>
<tr><td>Hematology</td><td colspan="3">1. Iron deficiency anemia (microcytic anemia) due to inadequate dietary intake and GIT blood loss.
2. Megaloblastic anemia due to folate deficiency, malnutrition and impaired folate absorption.
3. Hemolytic anemia. (Destruction of red blood cells)
4. Bone marrow suppression.
5. Thrombocytopenia (suppressing platelet formation and prolong bleeding time).
6. Impaired production of vitamin-K dependent clotting factors leading to prolonged prothrombin time. (Vit K is an important precursor to clot if there were deficiency thrombocytopenia will happen)</td></tr>
<tr><td rowspan="3">Endocrine</td><td rowspan="2">Hypogonadism</td><td>In women</td><td>ovarian dysfunction, amenorrhea (abnormal absence of menstruation) , anovulation, hyperprolactinemia (high prolactin) associated with low estrogen →infertility.</td></tr>
<tr><td>In men</td><td>Gynecomastia, decreased muscle and bone mass, testicular atrophy and sexual impotence due to inhibition of luteinizing hormone (LH), decreased in testosterone, estradiol and progesterone.</td></tr>
<tr><td>Hypoglycemia & ketoacidosis</td><td colspan="2">due to impaired hepatic gluconeogenesis & excessive lipolytic factors, especially increased cortisol and growth hormone.
Ketoacidosis can be seen in 2 condition if the glucose is :
- Low : alcoholism patient (fatty liver)
- High : diabetic patient</td></tr>
<tr><td>CNS</td><td colspan="3">1. Tolerance.
2. Physiological and psychological dependence.
• Physiological dependence: Changes in physiological action according to the substance the patient’s addicted to it.
• Psychological dependence: No changes in the physiology but the person just want to show off.
3. Addiction: dopamine, serotonin and opioids are involved
4. Neurological disturbances.
5. Wernicke-Korsakoff syndrome. Vitamins deficiency→ A,D,B”B1”→ Wernicke encephalopathy or Korsakoff psychosis may occur</td></tr>
</table>

Chronic Alcoholism Associated Syndromes

Fetal alcohol syndrome(FAS)

- are a group of conditions that can occur in a person whose mother drank alcohol during pregnancy.
- Problems may include an **abnormal appearance, short height, low body weight, small head size, poor coordination, low intelligence, behavior problems, and problems with hearing or seeing.**
- **Irreversible syndrome**
- Ethanol rapidly crosses placenta and it's prohibited in all pregnancy trimesters.
- Prenatal exposure to alcohol causes:
  1. **Intrauterine growth retardation (reduction in body weight) due to hypoxia.**
  2. **Congenital malformation** (**Teratogenic effects**) such as:
     - Microcephaly. (small brain)
     - Impaired facial development.
     - Congenital heart defects.
     - Physical and mental retardation.



Wernicke-Korsakoff syndrome

It is a combined manifestation of 2 disorders:

Wernicke's encephalopathy	**Korsakoff's psychosis:**
characterized by: 1. ocular disturbances 2. unsteady gait 3. changes in mental state as confusion, delirium (هذيان), ataxia	1. Impaired memory especially in elderly. 2. Cognitive and behavioral dysfunction.

Cause: **thiamine (vitamin B1) deficiency** (rarely seen with absence of alcoholism) due to:

- inadequate nutritional intake.
- **decreased** uptake of thiamine from GIT.
- **decreased** liver thiamine stores.

Treated by: **thiamine + dextrose-containing IV fluids. (because of dehydration).**

Alcoholism Tolerance

Chronic consumption of alcohol leads to tolerance That develops due to:

Metabolic tolerance (pharmacokinetic)	**Due to induction (increase) of liver microsomal enzymes (e.g. CYP450) in chronic use.**
Functional tolerance (Pharmaco-dynamic)	**Changes in CNS sensitivity of receptors to dopamine and GABA mainly.**

Alcoholism withdrawal symptoms

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

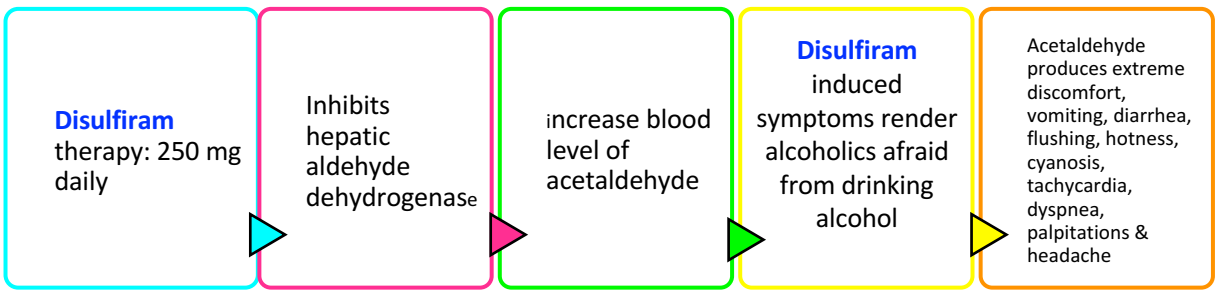
- Autonomic hyperactivity & craving for alcohol
- Vomiting, thirst
- Profuse sweating, severe tachycardia
- Vasodilatation, fever
- Delirium, tremors, anxiety, agitation, insomnia (CNS effects and need to be controlled)
- transient visual/ auditory illusions, violent behavior, hallucinations.
- Grand mal **seizures** (after 7-48 hours of alcohol cessation) Due to **super-sensitivity of glutamate receptors** & **hypo-activity of GABA receptors** are possibly involved.

Management of alcoholism withdrawal

Substituting alcohol with a long-acting sedative hypnotic drug (depressant drug) then tapering the dose

Benzodiazepines	as (**Chlordiazepoxide**, **diazepam**) →long acting drug. Or **lorazepam** that is ***preferable*** (***shorter*** duration of action)
	Dose of benzodiazepines should be carefully adjusted To provide Efficacy: (**IV/ po**) &Manage **withdrawal symptoms** & prevent irritability, insomnia, agitation & seizures. & avoid **excessive dose** that causes respiratory depression & hypotension.
Fluoxetine	• Serotonin reuptake inhibitor (anti-depressant drug). • Affect dopamine levels.
Clonidine & Propranolol	**Clonidine** is a2 agonist **inhibits** the action of exaggerated **sympathetic activity.**
Acamprosate	a weak **NMDA receptor antagonist & GABA activator**, reduce psychic craving (reduce risk of relapse)

To prevent alcohol relapse



Alcohol and drug interactions

Acute alcohol use (large dose)	causes **inhibition** of liver microsomal enzyme, decreases metabolism of some drugs and increases their toxicities e.g. **bleeding** with **warfarin**
Chronic alcoholuse(continuous dose)	**induces** liver microsomal enzymes and increases metabolism of drugs such as **warfarin, propranolol** and etc
other	• **Acetaminophen** + alcohol (chronic use)= risk of **hepatotoxicity**. →due to increased production of free radical metabolite of acetaminophen→High metabolism of high doses of acetaminophen →high free radicals (result from metabolismby microsomal enzymes) →hepatotoxicity • **NSAIDs + alcohol:** Increase in the risk of developing a major GI bleeding or an ulcer. Because NSAIDs may causes ulcer and bleeding, so the combination increases the risk of ulcer & bleeding • Narcotic drugs (**codeine** and **methahdone**) + alcohol= risk of **respiratory and CNS depression** • Alcohol suppresses gluconeogenesis, which may increase risk for hypoglycemia in diabetic patients.

إِنَّ فِي ذَٰلِكَ لَآيَاتٍ لِّقَوْمٍ يَتَفَكَّرُونَ ﴿٣﴾

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إبراهيم فتياني

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