pharmacology
Team 438

MED438

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Neuropsychiatry Block

Pharmacology Team 438

Alcohol and The Brain

Objectives

By the end of the lecture , you should know:

- 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 alcohol at different organ levels
- Describe the additive 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:

Black : Main content
Red : Important
Blue: Males' slides only
Pink : Females' slides only
Grey: Extra info or explanation
Green : Dr. notes

Editing File

Ethyl Alcohol (ethanol)

Pharmacokinetics

- Most commonly abused drug in the the world.
- 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).
- 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**[1] (Drug interactions).

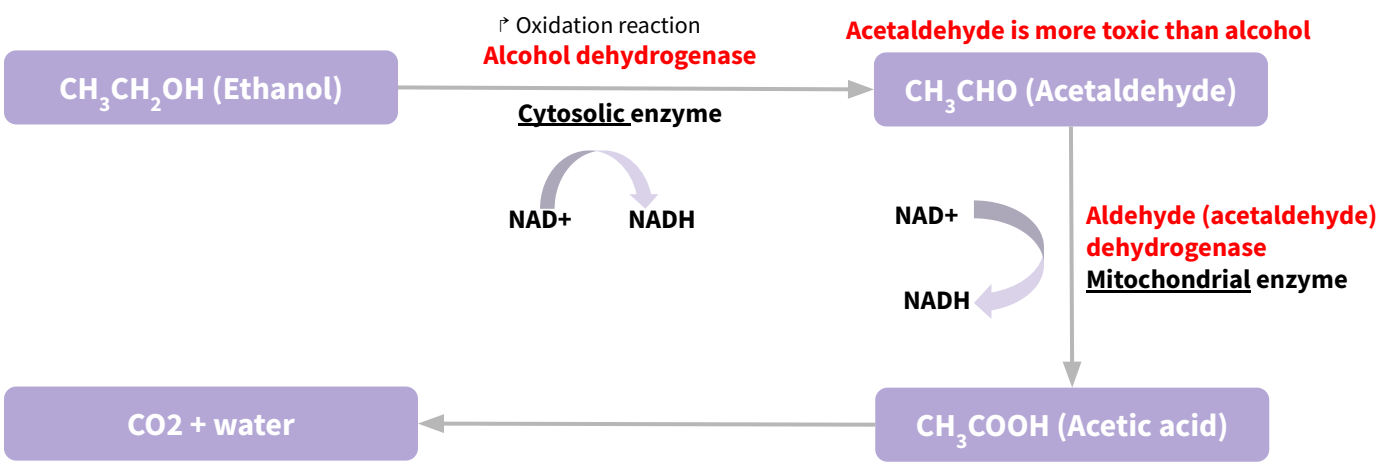
Metabolism in gastric mucosa and liver

- Oxidation[2] 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 NADH.
- Acetate ultimately is converted to **CO2** + 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**.

Alcohol metabolism

A) 90-98% in the liver (the major pathway)

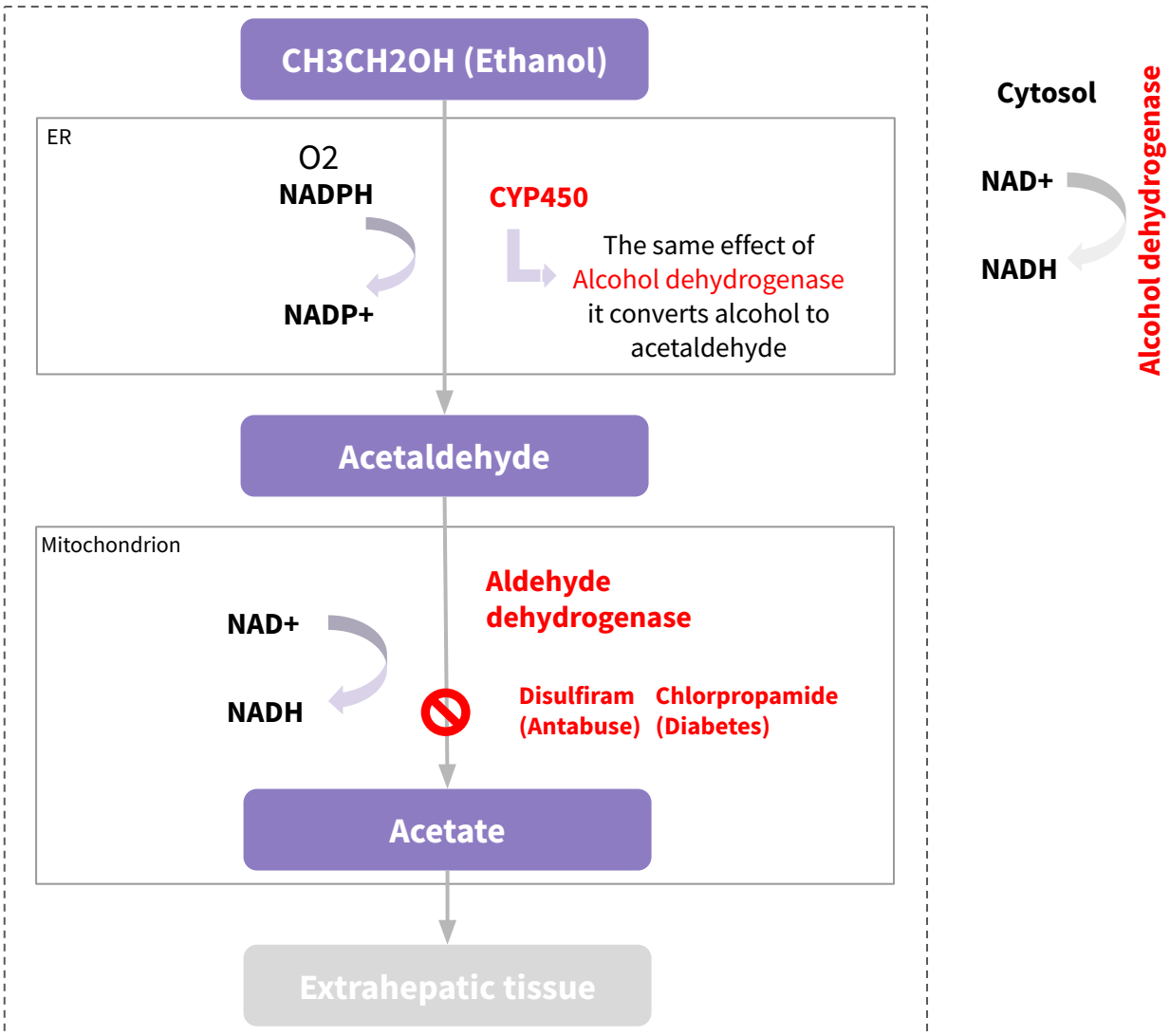
Depends on cytosolic enzyme (alcohol dehydrogenase)



1. Warfarin metabolism increase → anticoagulant effect decrease .
2. Alcohol oxidation yields aldehydes (acetaldehyde), aldehyde oxidation yields a carboxylic acid (acetate)

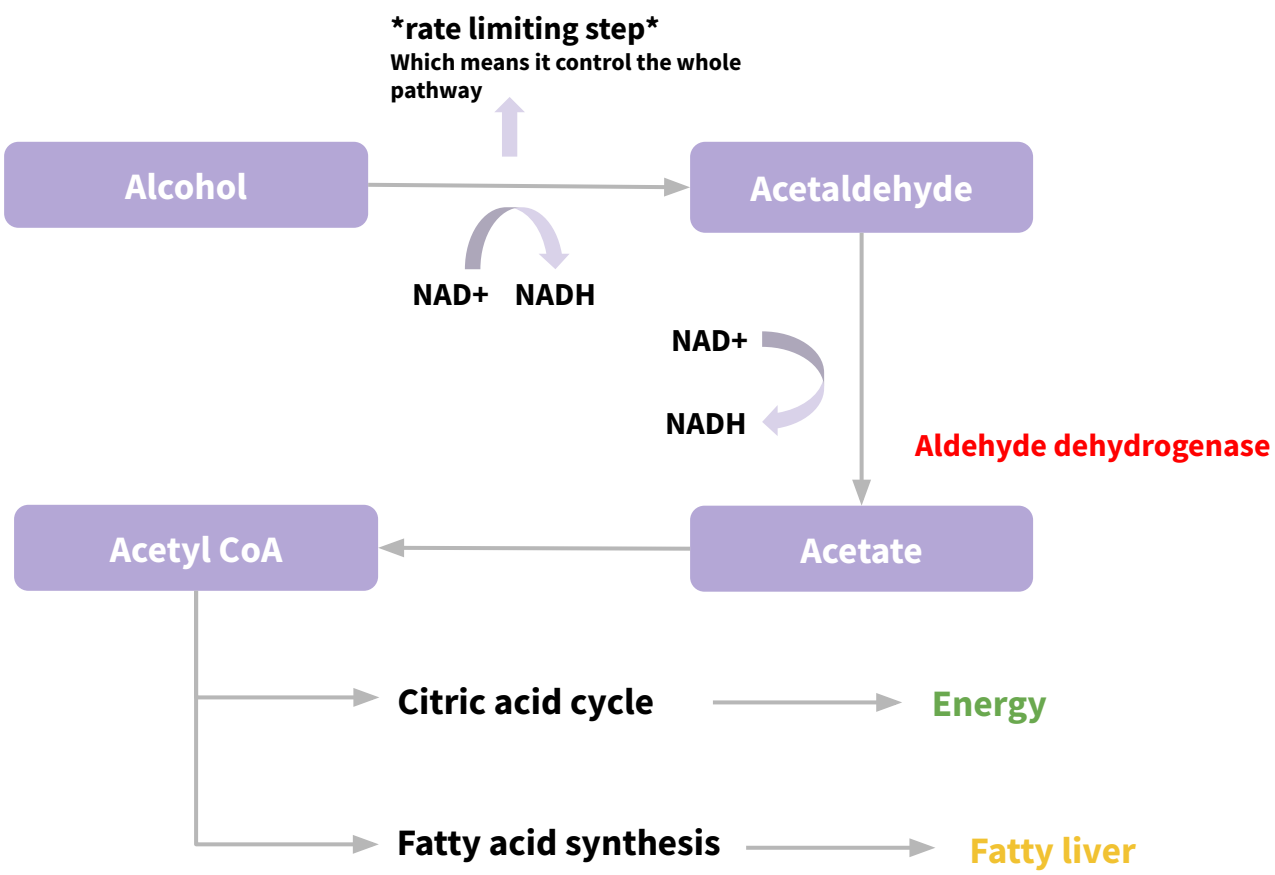
B) Hepatic cellular processing of alcohol (Minor pathway):

(depends on the microsomal enzymes)



Girls slides

Hepatic ethanol metabolism:



Genetic variation of alcohol metabolism

Aldehyde dehydrogenase polymorphism[1]:

- **Asian** populations have genetic variation in **aldehyde dehydrogenase** resulting in a variant allele.
- The rate of metabolism of alcohol is **slower** than other populations.
- Can develop **"Acute acetaldehyde toxicity"** after alcohol intake. **characterized** by **nausea, vomiting, dizziness, headache, vasodilatation, and facial flushing** (prevent them from becoming alcoholic.)

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

Mechanism of action of alcohol:

Alcohol is a CNS depressant

Acute alcohol[2]	Chronic alcohol
• **Enhancement of the effect of GABA** (inhibitory neurotransmitter) **on its GABA receptors** in brain leading to CNS depression. • **Inhibition of glutamate action** (excitatory neurotransmitter) **on NMDA** (N-methyl-d-aspartate) **receptors** leading to disruption in memory, consciousness, and alertness.	• **Up-regulation[3] of NMDA receptors** & **voltage sensitive Ca_{2+} channels** (Ca_{2+} influx to nerve cells). • Leading to **alcohol tolerance & withdrawal symptoms** (tremors, exaggerated response & seizures). • Down regulation of GABA.

1. Polymorphism means that a specific protein is encoded by different variations of a gene within the population, however the function of the protein remains largely the same.
2. Only single administration "dose"
3. Up-regulation means increase number of receptors " mainly " or increase receptor activity. when effect of alcohol decreases from the body, glutamate effect will be exaggerated due to the increase number of receptors leads to withdrawal symptoms.

Acute actions of alcohol

In mild-moderate amounts

CNS depression:

- Relieves anxiety, euphoria (feeling of well-being).
- 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 depression
- Respiratory acidosis
- Nausea, vomiting, aspiration of vomitus
- CVS depression
- Volume depletion
- **Hypotension**
- Hypothermia
- Coma,death

Chronic actions of alcohol

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

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

Liver	CVS	Hematology
1. Hepatic cirrhosis. 2. Liver Failure.	1. Hypertension. 2. Myocardial infarction.	1. Hematological disorders. 2. Neoplasia.
GIT	**CNS**	**Endocrine**
1. Irritation. 2. inflammation. 3. Bleeding. 4. Nutritional deficiencies.	1. Cerebral atrophy. 2. cerebellar degeneration. 3. peripheral neuropathy. 4. Wernicke encephalopathy or Korsakoff psychosis may occur.	1. Gynecomastia. 2. testicular atrophy.

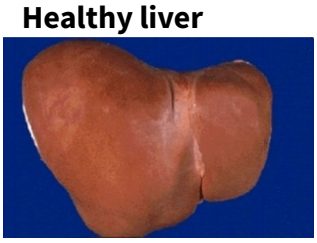
Complications of chronic alcohol use (Alcoholism)

Liver

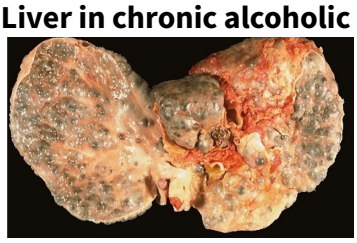
The most common medical complication occurs with liver:

- Reduction of gluconeogenesis (decrease glucose conc.) → Hypoglycemia
- Fatty liver/ alcoholic steatosis
- Hepatitis
- **Hepatic cirrhosis:** jaundice, Ascites, bleeding, encephalopathy.
- Irreversible liver failure.

Healthy liver



Liver in chronic alcoholic



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

Healthy liver vs fatty liver

<u>- Alcoholic Liver Disease:</u>
Normal Liver ⇆Steatosis[1] ⇆Steatohepatitis[2] ⇆Cirrhosis[3]

GIT system

- **Direct toxic action on epithelium causes :** Gastritis, hemorrhagic esophagitis, ulcer diseases, pancreatitis
- Diarrhea
- Deficiency of vitamins.
- Exacerbates nutritional deficiencies
- weight loss, and malnutrition (due to malabsorption)
- In heavy drinkers: increased risk of oral and esophageal cancer.

1-(infiltration of liver cells with fat)
2-(inflammation of the liver with concurrent fat accumulation in liver)
3- (a chronic disease of the liver marked by degeneration of cells, inflammation, and fibrous thickening of tissue).

Complications of chronic alcohol use (Alcoholism)

CVS System	• Chronic alcohol abuse can lead to cardiomyopathy • Cardiac hypertrophy • Congestive heart failure. • Arrhythmia due to K+ and Mg2+ depletion • Hypertension due to increased Ca2+ & sympathetic activity and destruction to endothelium
Hematological complications	• Iron deficiency anemia[1](due to inadequate dietary intake & GIT bleeding). • Megaloblastic anemia: (due to folate deficiency, malnutrition, impaired folate absorption). • Hemolytic anemia[2]. • Bone marrow suppression • Thrombocytopenia (suppressing platelet formation, prolong bleeding times). • **Impaired production of vitamin-K dependent clotting factors** leading to prolonged prothrombin time.
Endocrine System	• **Hypogonadism**[3] **-** 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**[4] due to impaired **hepatic gluconeogenesis** & excessive lipolytic factors, especially increased **cortisol and growth hormone.**
CNS	• Tolerance • Physiological and psychological dependence • Addiction: dopamine, serotonin and opioids are involved. • Neurologic disturbances • Wernicke-Korsakoff syndrome

1- also called microcytic hypochromic anemia .
2- rupture to RBC due to 1- hypophosphatemia 2- change in RBC cell membranes , RBC become fragile
3- reduction or absence of hormone secretion or other physiological activity of the gonads (testes or ovaries)
4- in diabetic patient ketoacidosis due to hyperglycemia , while in alcoholic patient due to hypoglycemia and overproduction of cortisol and growth hormone

Chronic alcoholism associated syndromes

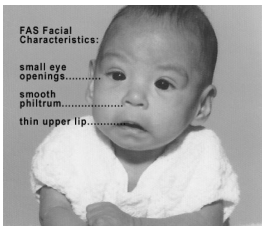
Fetal Alcohol Syndrome (FAS): Irreversible

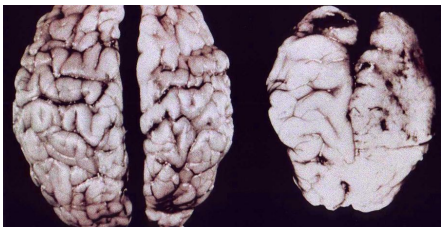
-Alcohol is the leading cause of mental retardation and congenital malformation.

-Ethanol rapidly crosses placenta → the fetal liver has little or no alcohol dehydrogenase → fetus must rely on maternal & placental enzymes for elimination

Prenatal exposure to alcohol causes:

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





The right brain is an infant's brain that had prenatal exposure to alcohol.

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, ataxia.	1. Impaired memory 2. Cognitive and behavioral dysfunction.

Cause: Thiamine (vit. B1) deficiency due to:

- Inadequate nutritional intake.
- Decreased uptake of Thiamine from GIT.
- Decreased liver Thiamine stores.

Treated by: Thiamine + dextrose-containing [1] IV fluids

Alcoholism Tolerance[2]

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

Metabolic tolerance (pharmacokinetic[3])	**Functional tolerance** (Pharmacodynamic[4])
due to induction of **liver microsomal enzymes e.g. CYP450**	due to **change in CNS sensitivity**

1- Dextrose to correct hypoglycemia
2- Differentiate between Pharmacokinetic and Pharmacodynamic (metabolic,functional respectively)
3- Change in the absorption,distribution, metabolism, excretion.
4-Change in the receptors.

Alcoholism withdrawal symptoms[1]

★ All these symptoms are due to super-sensitivity of **glutamate receptors** & Hypo-activity of **GABA receptors** are possibly involved.

- 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** (after 7-48 hr alcohol cessation).

Management of Alcoholism Withdrawal

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

- **Benzodiazepines** — as chlordiazepoxide, diazepam Or (lorazepam that is **preferable shorter** duration of action)
- **Fluoxetine** — increases serotonin level and decreases dopamine (Serotonin reuptake inhibitors)
- **Clonidine and Propranolol** — inhibits the action of exaggerated sympathetic activity
- **Acamprosate**[2] — weak NMDA receptor antagonist & GABA activator ⟶ reduce psychic craving

1-**-**for treatment : we give them GABA agonist or glutamate antagonist,major cause of withdrawal symptoms is high glutamate and low GABA .
2-mimicking alcohol but without addiction and with less side effects.

To prevent alcohol relapse:

Disulfiram therapy 250 mg daily.

It Inhibits hepatic **aldehyde dehydrogenase** →increase blood level of **acetaldehyde**

Disulfiram: induced symptoms render alcoholic afraid from drinking alcohol

Acetaldehyde produces extreme discomfort vomiting, diarrhea, flushing, hotness, cyanosis, tachycardia, dyspnea, palpitations & headache

Alcohol and drug interactions

Acute Alcohol use VS Chronic Alcohol use

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

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

1. **Acetaminophen**[1] + alcohol (chronic use)= risk of **hepatotoxicity** due to increased production of free radical metabolite of acetaminophen
2. **NSAIDs** + alcohol = Increase in the risk of developing a **major GI bleed** or an **ulcer.**[2]
3. **Narcotic drugs (codeine and methadone)** + alcohol = risk of **respiratory and CNS depression**
4. Alcohol **suppresses gluconeogenesis,** which may increase risk for **hypoglycemia in diabetic patients.**

1. Paracetamol metabolism yields small amounts of NAPQI, a free radical. Which is detoxified in the liver. Overdose causes toxicity due to its accumulation. Treatment: N-acetylcysteine.
2. Bc NSAIDs may causes ulcer and bleeding, so the combination increases the risk of ulcer & bleeding

Quiz

MCQ

1. A 56 year old Russian man, chronic alcoholic, came to the the emergency clinic with symptoms of Wernicke-Korsakoff Syndrome. What is the treatment?
   (A)Thiamine + Dextrose containing IV fluids. (B)Benzodiazepines
   (C)Methoxyflurane (D)Pilocarpine

2. 48 year old man , alcoholic, was given an NSAID by the doctor , which of the following risks will increase?
   (A) Increase liver function tests (B)Peptic ulcer
   (C)Hypocalcemia (D) Hypercalcemia

3. A 28 year old saudi man coming from a party, caught by police at midnight, showing anxiety , ataxia, slurred speech and impaired judgment, which of the following is caused by the acute use of alcohol?
   (A) inhibition of liver enzymes (B) Induction of liver enzymes
   (C)enhance action of glutamate (D) Upregulation of NMDA receptors

4. A 57 year old women, wants to quit alcohol, what is the best treatment for her and to prevent her from drinking again?
   (A)Benzodiazepines (B)Disulfiram
   (C) Acamprosate (D)Paracetamol

5. Deficiency which of the following is associated with Wernicke-Korsakoff Syndrome?
   (A) B1 (B)folate
   (C)B12 (D)B2

SAQ

Q1: A 63 years old patient with unsteady gait, impaired memory and ocular disturbances, he drinks whisky regularly, what is the diagnosis of his condition?

Q2: Based on Q1, give two causes of the patient condition?

Q3: Based on Q1, what is the treatment?

Q4: Give 2 drugs Contraindicated with Chronic alcoholism?

Q5: Give 3 symptoms of alcoholism withdrawal?

Answers:

MCQ

Q1	A
Q2	B
Q3	A
Q4	B
Q5	A

SAQ

Q1	Wernicke-Korsakoff syndrome
Q2	**1-** Decreased uptake of Thiamine from GIT **2-** Decreased liver Thiamine stores
Q3	Thiamine + Dextrose containing IV fluids.
Q4	**1-** Warfarin **2-** Acetaminophen
Q5	**1-** Vomiting **2-** hallucinations **3-**Grand mal seizures

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Team 438

Good Luck , Future Doctors!

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Share with us your ideas !