MED 443
King Saud University

Lama AlMutairi
تمت المراجعة
٤٤٣
Mohammed AlEssa
Abdulaziz AlFuhaid

TEAM 443
PHARMACOLOGY

Alcohol and the brain

- Main text
- Male slide
- Female slide
- Important
- Dr, notes
- Extra info

EDITING FILE

Objectives

No objectives

Ethyl Alcohol (Ethanol)

Pharmacokinetics

- Most commonly **abused** drug in the the world
- Small **lipophilic** molecule
- Readily crosses all biological membranes "Blood brain barrier, placenta…"
- Rapidly & completely **absorbed from GIT**
- Has large Vd (distributed to all body tissues).
  Volume of distribution=total body water (0.5-0.7L/kg).
- Crosses placenta and excreted in milk

Acute alcohol consumption

inhibits CYP450 2E1 so decrease metabolism of other drugs taken concurrently as **(warfarin, phenytoin).**

↑DOA of warfarin→ Risk of bleeding

Chronic alcohol consumption

Induces liver **microsomal enzyme CYP450 2E1**,
which leads to significant increase in:
- **ethanol metabolism (Tolerance)**
-metabolism of other drugs as warfarin taken with it **(Drug interactions).**
↓ DOA of warfarin → Risk of thrombosis

Important

Metabolism of ethanol
(in Gastric Mucosa and Liver)

Oxidation of ethanol to **acetaldehyde** via **alcohol dehydrogenase** or CYP-450 (CYP-2E1).

➔ **At low ethanol conc.:** (Major metabolism by alcohol dehydrogenase) minor metabolism by microsomal ethanol-oxidizing system **(MEOS)** mainly **CYP-450** (CYP2E1).

➔ **Upon continuous alcohol use**: this enzyme is stimulated and contribute significantly to **alcohol metabolism & tolerance.** (Major metabolism).

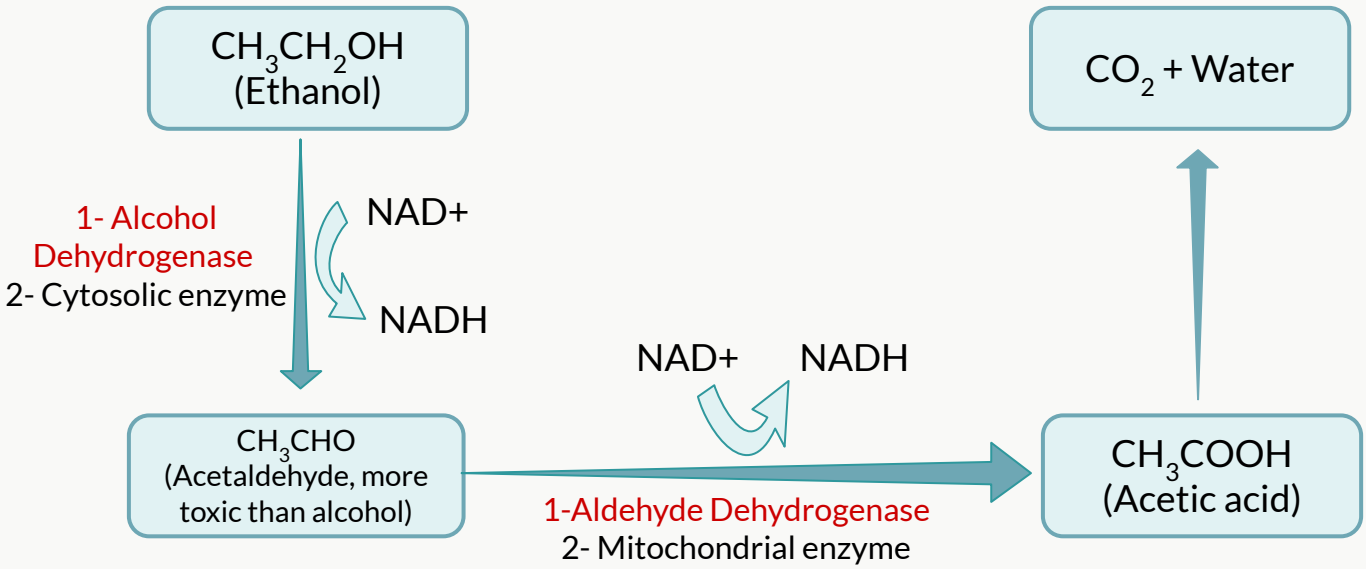
Acetaldehyde is more toxic than alcohol "causes tachycardia, nausea, vomiting, nervousness"

Oxidation of acetaldehyde to **acetate** via **aldehyde dehydrogenase** which also reduces NAD+ to NADH.

Acetate ultimately is converted to **CO2 + water** "This how it becomes harmless (end of effect)"

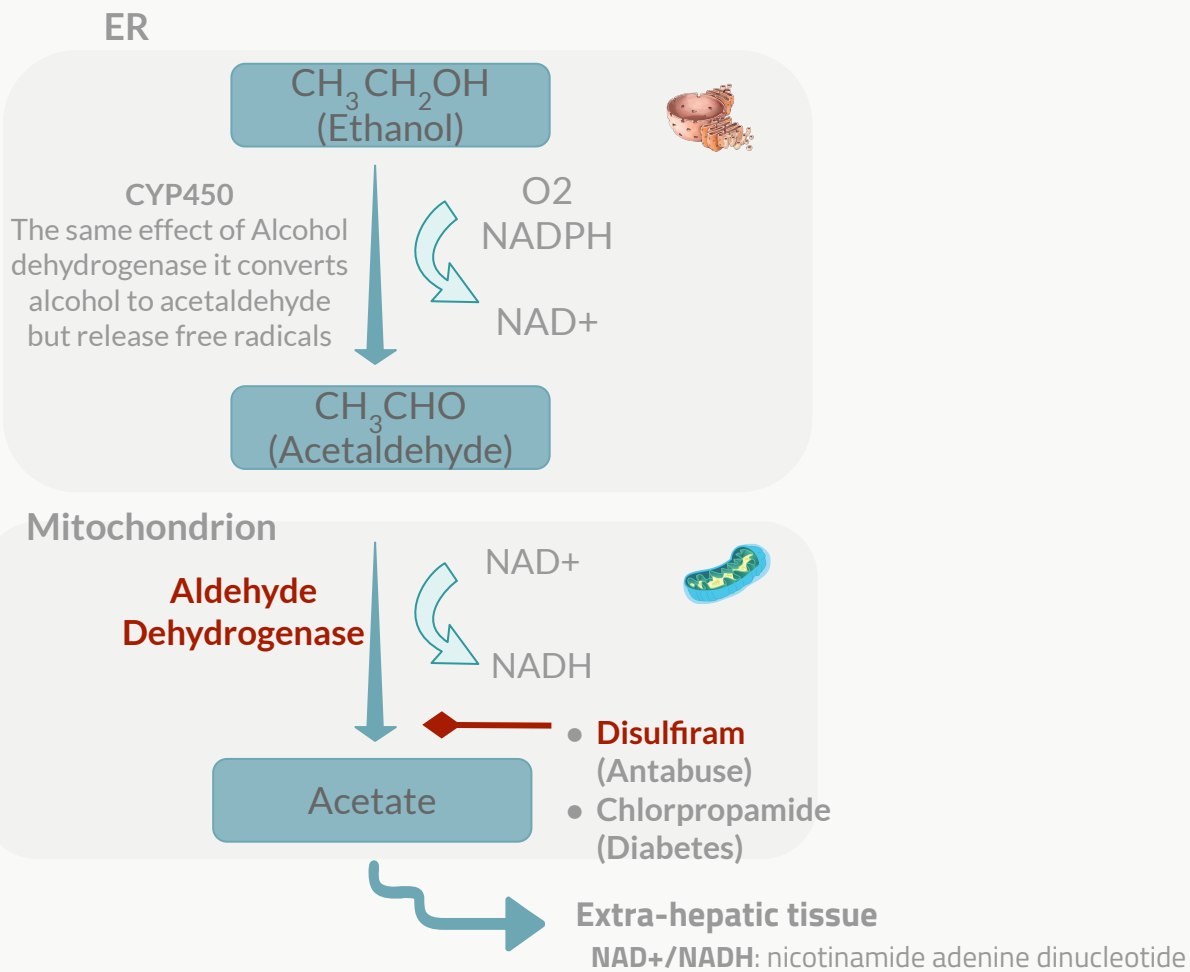
Alcohol Metabolism

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



B) Hepatic cellular processing of alcohol (minor pathway)

Extra
But important



NAD+/NADH: nicotinamide adenine dinucleotide

Extra

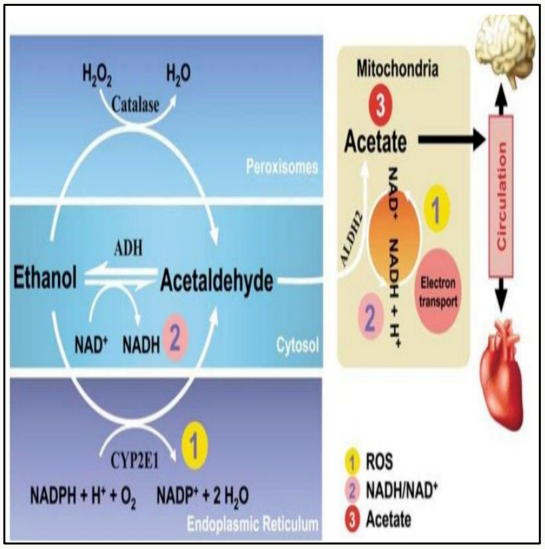
The hepatic cellular processing of alcohol include 3 pathways:

1- minor pathway at ER: Ethanol transformed to **Acetaldehyde** by **CYP450 (CYP2E1)** & NADPH & CO_2 & H^+ (giving NADP+ & $2H_2O$)

2- major pathway at cytosol: Ethanol transformed to **Acetaldehyde** by **Alcohol dehydrogenase** & NAD+ (giving NADH).

3- Accessory pathway at peroxisomes: Ethanol transformed to Acetaldehyde by **Catalase** & H2O2 (giving H2O)

Then all resulting acetaldehyde will go to mitochondria and transformed to **Acetate** by **Aldehyde dehydrogenase** & NAD+ (becoming NADH). The acetate finally will go to Extrahepatic tissues via circulation.



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.
- The rate of metabolism of alcohol is slower than other populations.
- Can develop **"Acute acetaldehyde toxicity"** after alcohol intake characterized by nausea, vomiting, dizziness, vasodilatation, headache, and facial flushing and protect against alcohol use disorder (AUD). (prevent them from becoming alcoholic.), This can happen in people who have no polymorphism but are on acetaldehyde metabolism inhibitors like metronidazole and disulfiram (disulfiram is used to stop addiction)

Alcohol Excretion

1. **Excreted unchanged in urine (2-8%).**
2. **Excretion unchanged via lung (basis for breath alcohol test).**
3. **Rate of elimination is: Zero-order kinetic** (no concentration-dependent.) i.e. rate of elimination is the same at low and high concentration have high risk of toxicity

Mechanism of action of alcohol

Alcohol is a CNS depressant

Acute alcohol leads to:

- Enhancement the effect of **GABA** (inhibitory neurotransmitter) on its **GABA receptors** in brain leading to **CNS depression**
- Inhibition of **glutamate** action (excitatory neurotransmitter) on **NMDA receptors** leading to **disruption in memory, consciousness, alertness.**

Chronic alcohol leads to

- **up-regulation** of NMDA receptors & voltage sensitive Ca^{2+} channels (Ca^{2+} influx to nerve cells) leading to **alcohol tolerance & withdrawal symptom** (tremors, exaggerated response & seizures)

Acute Actions of Alcohol

A) In mild-moderate amounts		B) In severe amounts
CNS depression	**CVS depression**	
• **Relieves anxiety**, euphoria (feeling of well-being). • Nystagmus, slurred speech, impaired judgment, ataxia • Sedation, hypnosis, loss of consciousness.	• Myocardial contractility depression • **Vasodilatation** due to: - Vasomotor center depression. - Direct smooth muscle relaxation caused by acetaldehyde.	• 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
- Hepatic cirrhosis
- Liver Failure

Hematological disorders, neoplasia.

CVS
- Hypertension
- Myocardial infarction

Endocrine
- Gynecomastia
- Testicular atrophy "lack of testosterone"

CNS
- Cerebral atrophy
- Cerebellar degeneration
- Peripheral neuropathy
- **Wernicke encephalopathy** or **Korsakoff psychosis may occur**

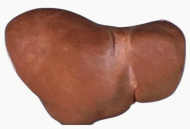
GIT "Damages gastric mucosa"
- Irritation.
- Inflammation.
- Bleeding
- Nutritional deficiencies → Anemia

Complications of Chronic Alcohol Use (Alcoholism)

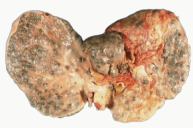
Liver

- The **most common** medical complication of alcoholism occurs with liver:
  - **Reduction of gluconeogenesis.**
  - **Fatty liver/ alcoholic steatosis**
  - **Hepatitis**
  - **Hepatic cirrhosis: jaundice, ascites, bleeding, encephalopathy.**
  - **Irreversible liver failure.**

Healthy Liver



Chronic alcoholics

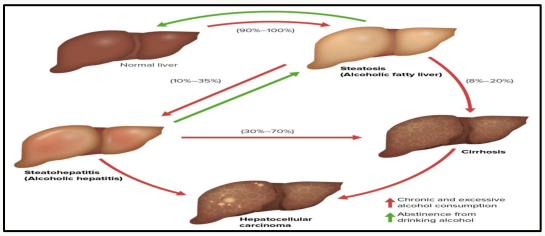


Acetaldehyde is more toxic than alcohol → causing inflammation and fat cell proliferation

Alcoholic Liver Disease

Normal Liver ⇄ Steatosis ⇄ Steatohepatitis ⇄ Cirrhosis

- **Alcoholic Liver Disease**



Cont.

GIT

- Gastritis, hemorrhagic esophagitis, ulcer diseases, pancreatitis (due to direct toxic action on epithelium).
- Diarrhea (increase motility)
- Deficiency of vitamins. - Especially lipid soluble vitamins (ADEK) -
- Exacerbates nutritional deficiencies
- Weight loss, and malnutrition
- In heavy drinkers: increased risk of oral and esophageal cancer.

Endocrine

- **Hypogonadism:**
  In women: ovarian dysfunction, amenorrhea , anovulation, hyperprolactinemia, infertility (hyperprolactinemia is always associated with infertility).
  In men: gynecomastia (enlargement of breast tissue), 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.

CVS

- Chronic alcohol abuse can lead to **cardiomyopathy**
  - Cardiac hypertrophy
  - Congestive heart failure
  - **Arrhythmia** due to potassium and magnesium depletion
  - **Hypertension** due to increased Calcium & sympathetic activity and destruction to endothelium

Hematological

- **Iron deficiency microcytic anemia** (due to inadequate dietary intake & GIT blood loss).
- **Megaloblastic anemia**: (due to folate deficiency, malnutrition, impaired folate absorption).
- **Hemolytic anemia** free radicals produced by acetaldehyde will damage the antioxidant membrane around the RBCs causing cell lysis
- **Bone marrow suppression**
- **Thrombocytopenia** (suppressing platelet formation, prolong bleeding times)
- Impaired production of **vitamin-K dependent clotting** factors leading to prolonged prothrombin time.

CNS

- Tolerance
- Physiological and psychological dependence
- Addiction: **dopamine, serotonin and opioids are involved** The rewarding NT's
- Neurologic disturbances
- **Wernicke-Korsakoff syndrome**

Chronic Alcoholism Associated Syndromes

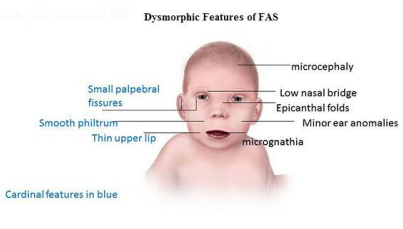
Important

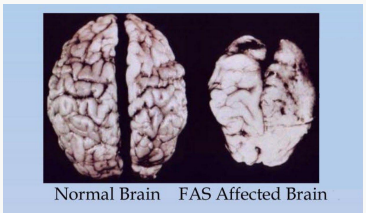
Fetal alcohol syndrome: irreversible

- Ethanol rapidly crosses placenta and fetal BBB

Pre-natal exposure to alcohol causes:

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





الطفل يعتبر كأنه عضو من الأعضاء للأم عشان كذا كل الكحول اللي تشربه بيروح له زيه وأول ما ينولد بتجيه أعراض انسحابية لأنه وقف يوصله كحول

Wernicke-korsakoff syndrome

It's a combined manifestation of two disorders:

Wernicke's encephalopathy

characterized by:

- **C**hanges in mental state as **c**onfusion,delirium
- **O**cular disturbances
- **A**taxia, unsteady gait
- Thiamine deficiency

Korsakoff's psychosis

- Impaired memory
- Cognitive & Behavioral dysfunction.
  Mental impairment

➔ **Cause: thiamine (vitamin B1) deficiency** due to:

1. inadequate nutritional intake
2. decreased uptake of thiamine from GIT "because of damage to mucosa"
3. decreased liver thiamine stores

➔ **Treated by:** thiamine + dextrose containing IV fluids.

Alcoholism Tolerance

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

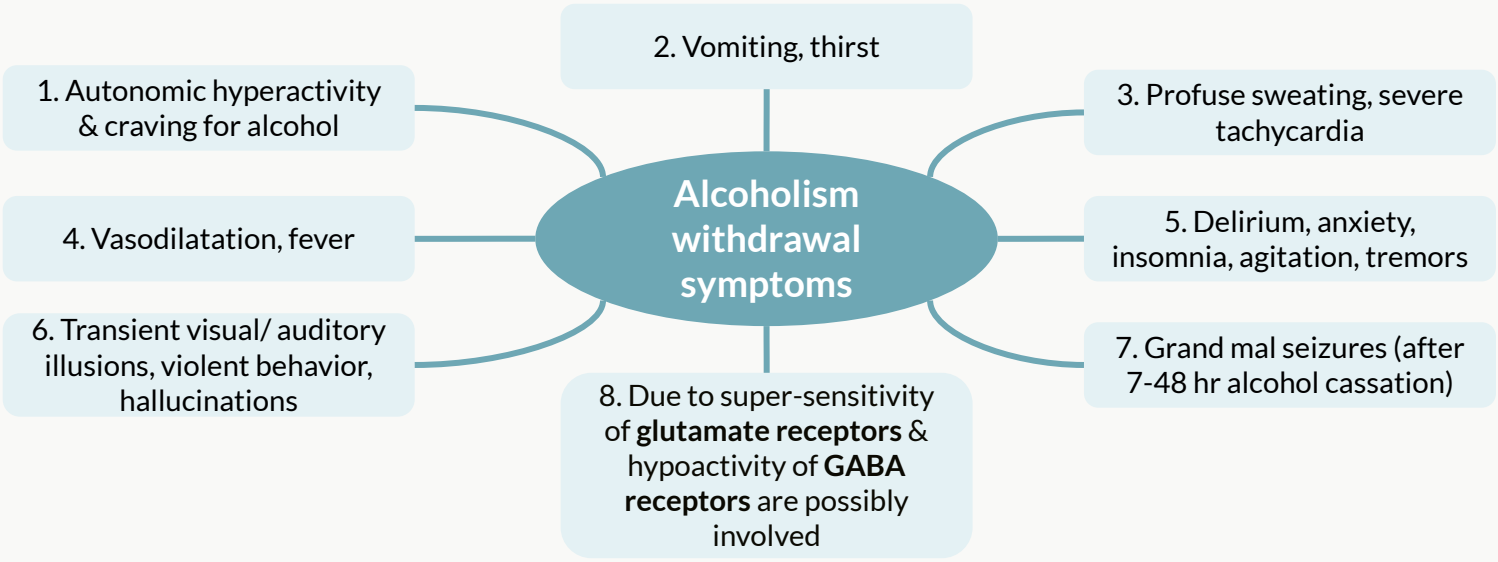
Metabolic tolerance (Pharmacokinetic)

- Due to induction of **liver microsomal enzymes.** (increases its own metabolism → needs higher doses for the same effect)

Functional tolerance (Pharmacodynamic)

- Due to **change in CNS sensitivity** upregulation of NMDA receptors and down regulation of GABA receptors

Alcoholism withdrawal symptoms



Management of alcoholism withdrawal

Substituting alcohol with a **long-acting sedative/hypnotic** drug then tapering the dose.

Benzodiazepines	• GABA enhancer, since its downregulated. • **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	Selective serotonin reuptake inhibitor (SSRI) Antidepressant which increases serotonin and dopamine.
Clonidine & propranolol	• Inhibits the action of exaggerated sympathetic activity.
Acamprosate	• Weak NMDA receptor antagonist & GABA activator→ reduces psychic craving. • Produces an effect similar to alcohol, without its other bad side effects.

To Prevent Alcohol Relapse:

1. **Disulfiram** therapy: 250 mg daily

- Disulfiram induced symptoms that render alcoholic afraid from alcohol drinking.
- It Inhibits hepatic **aldehyde dehydrogenase**→ increased blood level of **acetaldehyde.**
- Acetaldehyde produces extreme discomfort, vomiting, diarrhea, flushing, hotness, cyanosis, tachycardia, dyspnea, palpitations & headache.

2. **Acamprosate:**

- A weak NMDA receptor antagonist & GABA activator
- Reduces psychic craving
- Reduces relapse drinking in abstinent individuals

Alcohol and drug interactions

Never combine CNS depressants (requires dose adjustments)

Acute Alcohol use	Chronic Alcohol use
causes inhibition of liver microsomal enzymes → 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

"The drugs mentioned have similar toxicity to alcohol → increase its side effects"

1. **Acetaminophen"Paracetamol" + 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 GIT bleed** or **ulcers.**

3. **Narcotic drugs (codeine** found in cough drugs **and methadone) + alcohol** = risk of **respiratory and CNS depression**

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

MCQ

1. Most effective to decrease withdrawal symptoms			
A. Disulfiram	B. Diazepam	C. Folic acid	D. Thiamine
2. Deficiency of which of the following is related to the wernicke-korsakoff syndrome with excessive alcohol intake (chronic alcohol intake)?			
A. Folate	B. Thiamine (B1)	C. Riboflavine (B2)	D. Cobalamine (B12)
3. One of the following neurotransmitters may be related to the addiction in alcohol abuse			
A. GABA	B. Ach	C. Dopamine	D. Glutamate
4. What is the best treatment for a woman who wants to quit alcohol and prevent it's relapse? *			
A. Diazepam	B. Fluoxetine	C. Disulfiram	D. Acamprosate
5. A 28 years old woman was advised by her doctor to quit alcohol during her pregnancy but she wasn't able to obey the doctor. Which one of the following malformations is liable to happen to her fetus?			
A. Microcephaly	B. Neural tube defect	C. Teeth defect	D. Renal damage

1: B 2: B 3: C 4: C 5: A

SAQ

01

Describe the mechanism of action of Alcohol

slide 6

02

Pre-natal exposure to alcohol causes?

Slide 9

03

if a patient took ibuprofen, while being a heavy alcohol drinker, What could happen?

Increase in the risk of developing a **major GIT bleed** or **ulcers.**

Team Leaders

Muhannad Al-otabi

Reema Almotairi

Sarah Alajaji

Maryam Alghannam

Team members

Abdulaziz Alamri

Faisal Alateeq

Nazmi M Alqutub

Sultan Almishrafi

Mohammed Maashi

Mohammed Alasmary

Nazmi A Alqutub

Ziad Alhabardi

Mohammed Alrobeia

Mohammed Alhudaithi

Sami Mandoorah

Omar Alamri

Mohammed Alqutub

Reena Alsadoni

Almas Almutairi

Fatimah Alghamdi

Lama Alotaibi

Salma Alsaadoun

Jouri Almaymoni

Faisal alzuhairy

Salma Alkhlassi

Huda bin jadaan

Manar Aljanubi

Wasan Alanazi

Jana Almutlaqah

Farah Abukhalaf

Norah Almalik

Rawan Alqahtani

Aroub Almahmoud

Remaz Almahmoud

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