Lecture 3

Alcohol and the brain

- Additional Notes
- Important
- Explanation –Extra-

Alcohol and Brain

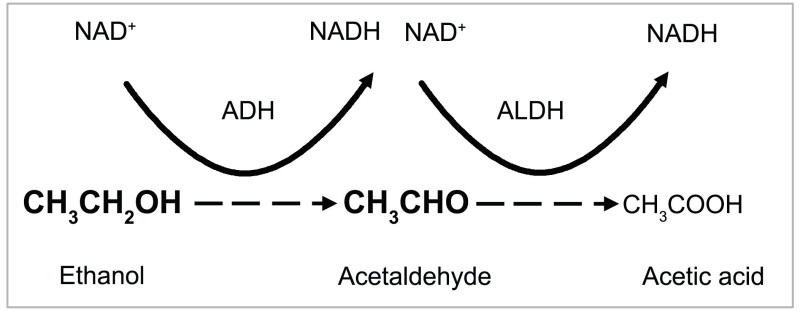
Ethyl alcohol (ethanol): is the most commonly abused drug in the world.
- We don't use alcohol as drugs, we'll just discuss pharmacological and toxic effects.

1-Pharmacokinetics.

- Small lipophilic molecule.
  - Small molecular weight + Lipophilic molecules = lipid soluble = can cross any cell membrane → cross BBB.
- Crosses all biological membranes.
- Rapidly and completely absorbed from GIT. It has complete absorption if it takes orally.
- Large Vd (distributed in all body tissues); Volume distribution = Total body water.
  - **Recall:** VD is mathematical factor to measure distribution of drug through body fluid "mainly total body water' so because here we have small molecule + lipophilic that is why it's = TBW.
- Crosses placenta excreted in milk. it will harm the fetus in pregnant and breast feeding
- **Acute alcohol consumption:** *inhibits* CYP450 2E1 so decrease metabolism of other drugs taken concurrently as (**warfarin**, **phenytoin:** anticonvulsant in the treatment of epilepsy).
- **Chronic alcohol consumption:** *induces* liver microsomal enzyme CYP450 2E1, which leads to significant increases in ethanol metabolism (Tolerance) & metabolism of other drugs as warfarin (increase risk of clot) = (Drug interactions).

2-Alcohol Metabolism. Metabolism in gastric mucosa & liver (mainly).

- Oxidation of ethanol to acetaldehyde (more toxic than alcohol) via alcohol dehydrogenase (ADH) or cyt-p450 (CYP2E1) → Acetaldehyde is converted to acetate via aldehyde dehydrogenase (ALDH) 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 alcohol use, this enzyme is stimulated and contribute significantly to alcohol metabolism & tolerance.



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 Asian populations don't have risk or reduced risk of addiction because they don't have the step" metabolism of Acetaldehyde " because the efficient of Aldehyde Dehydrogenase less than other people "not work properly' → accumulation of Acetaldehyde " will not transform to acetate"
  - 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 and prevent them from becoming alcoholic.

3-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) i.e. rate of elimination is the same at low and high concentration.

4-Mechanism of Action.

is a CNS depressants

Acute alcohol causes:

1. Enhance the effect of GABA (inhibitory neurotransmitter) on its GABA receptors in brain → CNS depression.
2. Inhibition of glutamate action (excitatory neurotransmitter) on NMDA (N-methyl-D-aspartate receptor) receptors leading to disruption in memory, consciousness, alertness.

Chronic alcohol leads to

Up-regulation of NMDA receptors & voltage sensitive Ca channels (Ca influx to nerve cells) leading to alcohol tolerance & withdrawal symptoms (tremors, exaggerated response & seizures).

Acute Action of Alcohol

❖ **In mild-moderate amounts:**

CNS depression. Degree of depression depend on the dose taken

- 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. Vasodilation → flush sensation

❖ **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) is associated with many complications:**

- Tolerance, dependence (physical & psychological), addiction, behavioral changes
- **Liver:** hepatic cirrhosis & liver failure.

Acetate converted to other product *Acetyl co A* "other than CO2+ H2O". In over drinking → consumption 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.

❖ **Most common medical complication occurs with liver.**

Fatty liver > inflammation > hepatitis > fibrosis "liver not functioning" > cirrhosis

- Reduction of gluconeogenesis Reduction of gluconeogenesis > accumulation of Acetyl co A > energy production from alcohol rather than from fat > accumulation of fat
- Fatty liver/alcoholic steatosis Hepatitis
- **Hepatic cirrhosis:** jaundice, ascites, bleeding, encephalopathy (liver metabolism not going properly>accumulation ammonia > enter brain > encephalopathy)
- Irreversible liver failure.

- **CVS:** hypertension (CVS damage of endothelium + NO "nitric oxide" inhibited >hypertension), myocardial infarction
- **CNS:** cerebral atrophy, cerebellar degeneration, and peripheral neuropathy. Wernicke encephalopathy or Korsakoff psychosis may occur. Vitamins deficiency> A,D,B"B1"> Wernicke encephalopathy or Korsakoff psychosis may occur.
- **GIT system:** irritation, inflammation, bleeding, nutritional deficiencies worsen the ulcer
- Endocrine system: gynecomastia & testicular atrophy
- Hematological disorders (all anemia types), neoplasia.

Alcoholism Complications

GIT System	1. Gastritis, hemorrhagic esopahgitis, ulcer diseases, pancreatitis (due to direct toxic action on epithelium), Diarrhea. 2. Deficiency of vitamins. (Vit A deficiency> alcohol dehydrogenase metabolize "retinol form" + Vit D deficiency>need to be in active form and this need a healthy liver + Vit B deficiency> cause CNS action) 3. Exacerbates nutritional deficiencies 4. weight loss, and malnutrition (weight loss > because there is no absorption). 5. In heavy drinkers : increased risk of oral and esophageal cancer.
CSV	**Chronic alcohol abuse can lead to <u>cardiomyopathy</u>** ▪ Cardiac hypertrophy ▪ Congestive heart failure. ▪ Arrhythmia (due to potassium and magnesium depletion) ▪ Hypertension: due to increased calcium & sympathetic activity.
Hematological Complications	• **Iron deficiency anemia** (due to inadequate dietary intake & GIT blood loss). • **Megaloblastic anemia**: (due to folate deficiency, malnutrition, impaired folate absorption). • **Hemolytic anemia**. • **Bone marrow suppression** • **Thrombocytopenia** (suppressing platelet formation, prolong bleeding times). • Impaired production of **vitamin-K dependent clotting factors** leading to prolonged prothrombin time.
Endocrine	❖ **Hypogonadism:** • **<u>In</u> women:** ovarian dysfunction, amenorrhea, anovulation, hyperprolactinemia, infertility. • **<u>In</u> 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 • Physiological and psychological dependence • Addiction: dopamine, serotonin and opioids are involved. • Neurologic disturbances • **Wernicke-Korsakoff syndrome**

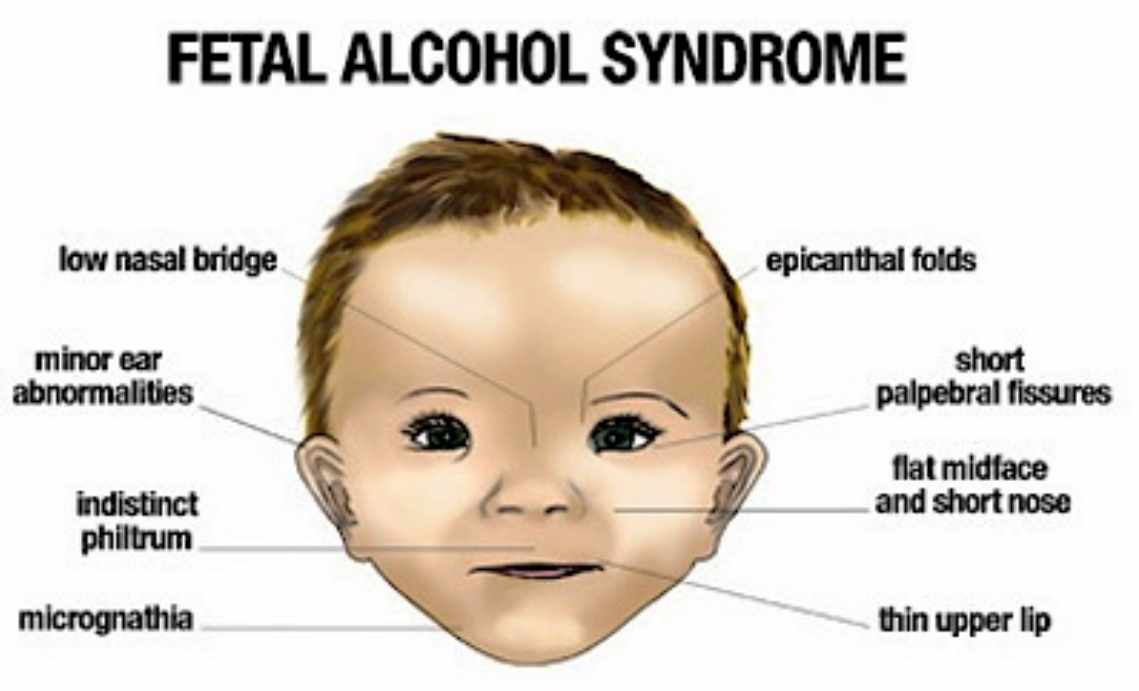
Alcoholism Associated Syndromes

Fetal Alcohol Syndrome (FAS): Irreversible

- ❖ Ethanol rapidly crosses placenta.

Pre-natal exposure to alcohol causes:

- Intrauterine **growth retardation** (due to hypoxia).
- 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:

- ocular disturbances - unsteady gait
- changes in mental state as confusion, delirium, ataxia

Korsakoff's psychosis:

- impaired memory & cognitive and behavioral dysfunction.
- **Cause:** thiamine (vitamin B1) deficiency
- **Treated by:** thiamine + dextrose-containing IV fluids

Alcoholism Tolerance	Alcoholism Withdrawal Symptoms	Management of Alcoholism Withdrawal
❖ **Chronic consumption of alcohol leads to tolerance that develops due to:** • Metabolic tolerance (pharmacokinetic): due to induction of liver microsomal enzymes. • Functional tolerance (Pharmacodynamics): due to changes in CNS sensitivity	• 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) • Due to super-sensitivity of glutamate receptors & hypoactivity of GABA receptors are possibly involved.	• 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**: (Beta blockers) 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	Others
• causes 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. • **Acetaminophen + alcohol** (chronic use)**:** risk of hepatotoxicity. (release free radicals) • **NSAIDs + alcohol:** Increase in the risk of developing a major GI bleed or an ulcer. • **Narcotic drugs (codeine and methahdone) + alcohol**: risk of respiratory and CNS depression.

Pharmacokinetics

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Summary

Minor metabolism of ethanol is done by MEOS " microsomal ethanol- oxidizing system " mainly is :

A) Cytochrome p450
B) Cytochorme p45
C) Cytochorme C20
D) Cytochorme a200

One of these drung has Zero-Order kinetic :

a) Wafferin
b) Pronolol
c) Ethnanol
d) Acamprosate

Acute using alcohol can lead to disruption in memory due to :

a) Increase effect of GABA
b) Decrease effect of GABA
c) Increase effect of glutamate
d) Decrease effect of gluatamate

Cause of hypertension in alcoholism is due to :

A) Decrease of Calcium
B) Increase parasympatic
C) Increase sympathic activity
D) Decrease sympathic activity

Alcoholism patient was suffering from sever foliate deficiency which type of anemia he will develop :

a) Megablastic anemia
b) Iron deficiency anemia
c) Hemolytic anemia
d) Aplastic anemia

one of complication of Alcoholism is Tolerance which of following is metabolic cause to develop tolerance :

a) Induction of liver microsomal enzymes
b) Increase of CNS sensitivity
c) Decrease of CNS sensitivity
d) Inhibition of liver microsomal enzymes

one of these drug is used to manage alcoholism withdrawal is :

a) Lorazepam
b) Codeine
c) Acetaminophen
d) Methahdone

Alcoholism having diabetic maltase which one the complication is increase to develop in his condition :

a) Hypogonadism
b) Liver fatty
c) Iron dificy anemia
d) Hypoglycemia

Disulfiram is used to pervert alcohol relapse which of these is MOA of this drug :

a) Inhabit Alchoal dehydrogenase
b) Incresae Alchoal dehydrogenase
c) Inhabit aldehyde dehydrogenase
d) Increase aldehyde dehyroganase

Alcoholic person whose using warfarin which of these drug – drug interaction will occur :

a) Bleeding
b) CNS depression
c) Hepatotoxicity
d) Hypoglycemia

Ans : A- C – D –C – A –A – A – D – C – A

Good luck!

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