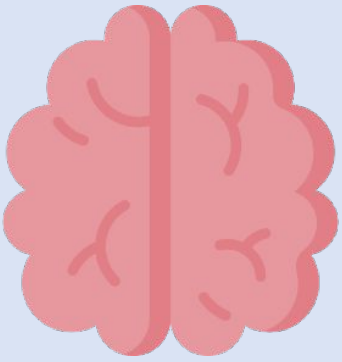

Revised & Approved

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Pharmacology 439

MED439

Neuropsychiatry Block

Pharmacology Team 439

Color index:

Main Text

Important

Dr's Notes

Female Slides

Male Slides

Extra

Alcohol and the Brain

Objectives:

1- Describe the pharmacological actions of alcohol
2- Describe the pharmacokinetic profile of alcohol
3- Describe the development of intoxication symptoms of alcohol
4- Describe how alcohol affects various neurotransmitters in the brain
5-Identify various toxicity of alcohol at different organ levels
6- Describe the additive nature of alcohol and its mechanism
7- Identify alcohol withdrawal symptoms and their management
8- Identify clinically relevant drug interactions with alcohol
9- Hazards of alcohol in pregnancy

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 (0.5-0.7L/kg). Distributed to all fluid compartments (ECF+ICF)
- Crosses placenta and excreted in milk (Affect pregnant & breast feeding)

- **Acute alcohol consumption** inhibits CYP450 2E1, ↓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 increases in ethanol metabolism (tolerance) & metabolism of other drugs as warfarin. (↓ DOA ⟶ Risk of thrombosis) (drug interactions).

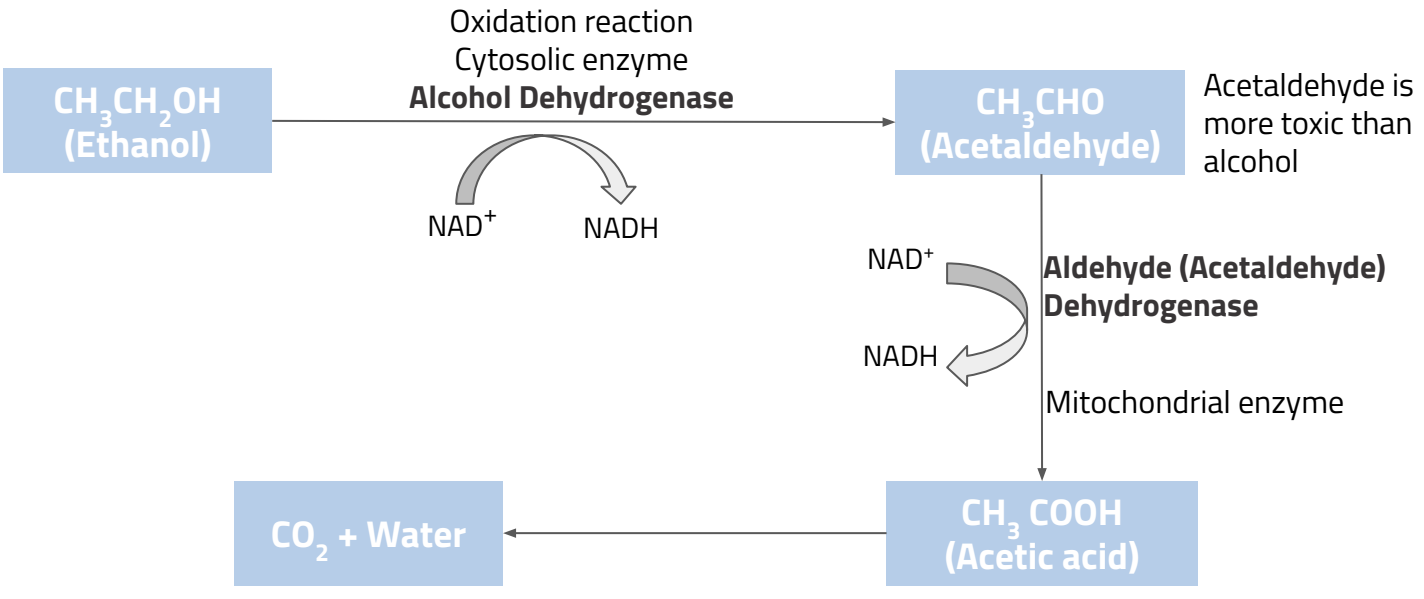
Metabolism in Gastric Mucosa and (predominantly) Liver

- Oxidation of ethanol to acetaldehyde via **alcohol dehydrogenase** (major) or cyt-p450 (minor)(CYP2E1).
- Acetaldehyde is converted to acetate (acid) via **aldehyde dehydrogenase** which also reduces NAD^+ to NADH. (both needs NAD as a cofactor to be reduced into NADH)
- Acetate ultimately is converted to CO_2 + water.
- **At low ethanol conc.** minor metabolism by MEOS (microsomal ethanol-oxidizing system) mainly cyt-p450 (CYP2E1).
- **Upon continuous** (chronic even at low doses) alcohol use, this enzyme is stimulated and contribute significantly to ↑ alcohol metabolism & tolerance.

Alcohol Metabolism

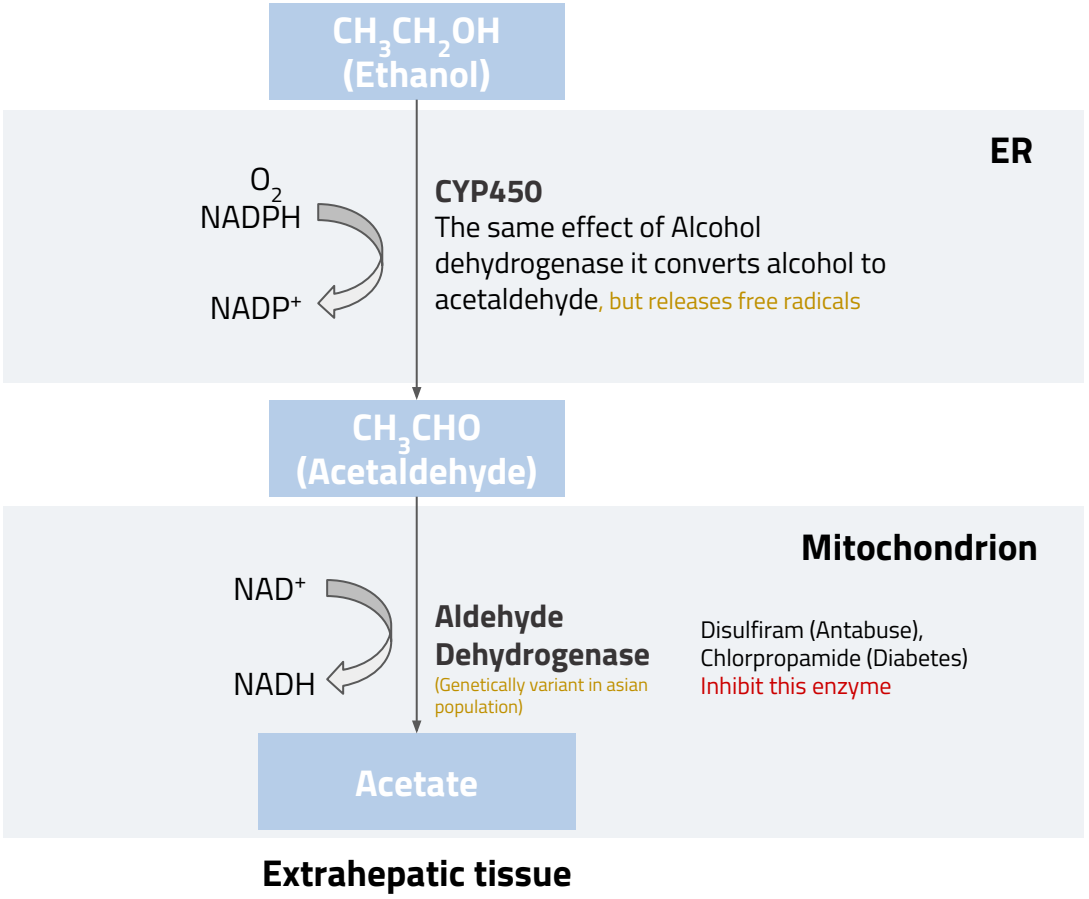
A) 90-98% in the liver (major pathway) at low concentration

Depends on cytosolic enzyme (alcohol dehydrogenase)



B) Hepatic cellular processing of alcohol (minor pathway) at high concentration

Depends on the microsomal enzymes.

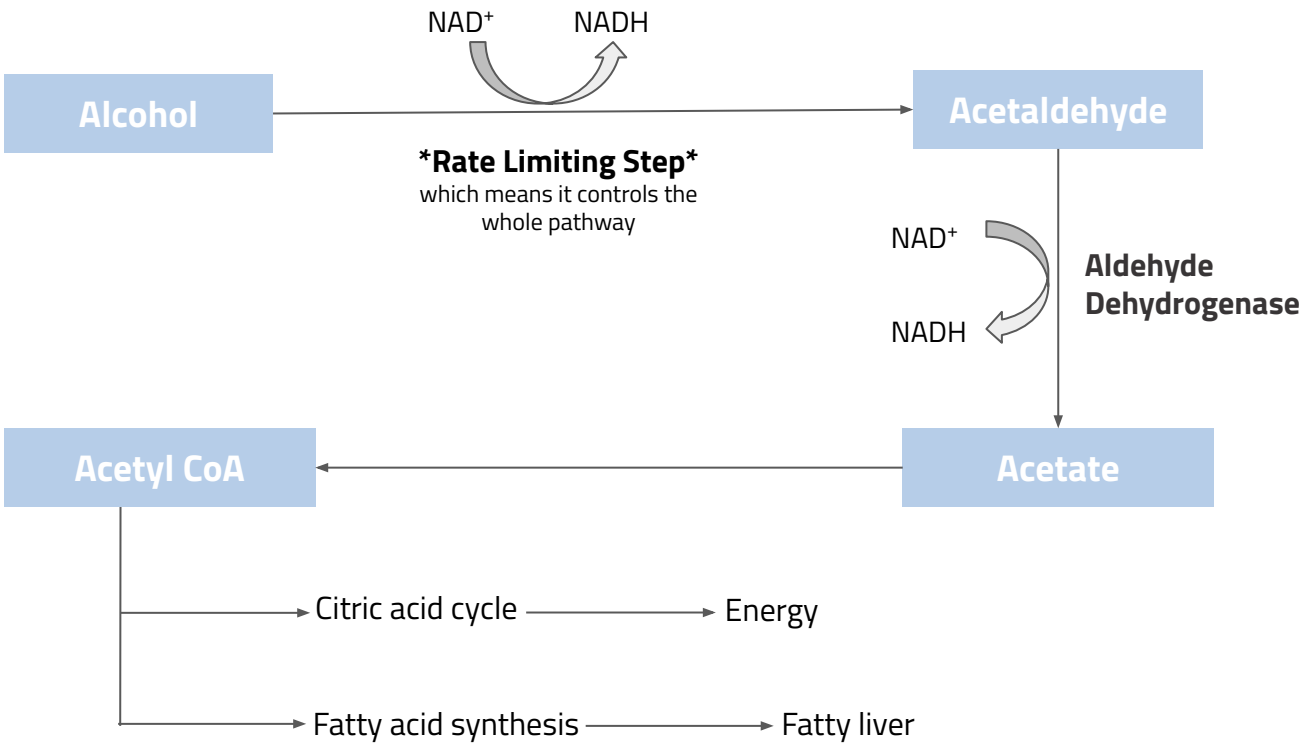


Low Ethanol conc. → minor metabolism by MEOS (CYP2E1)

Chronic use (high or low conc.) → induce metabolism by MEOS (CYP2E1)→ tolerance → addiction

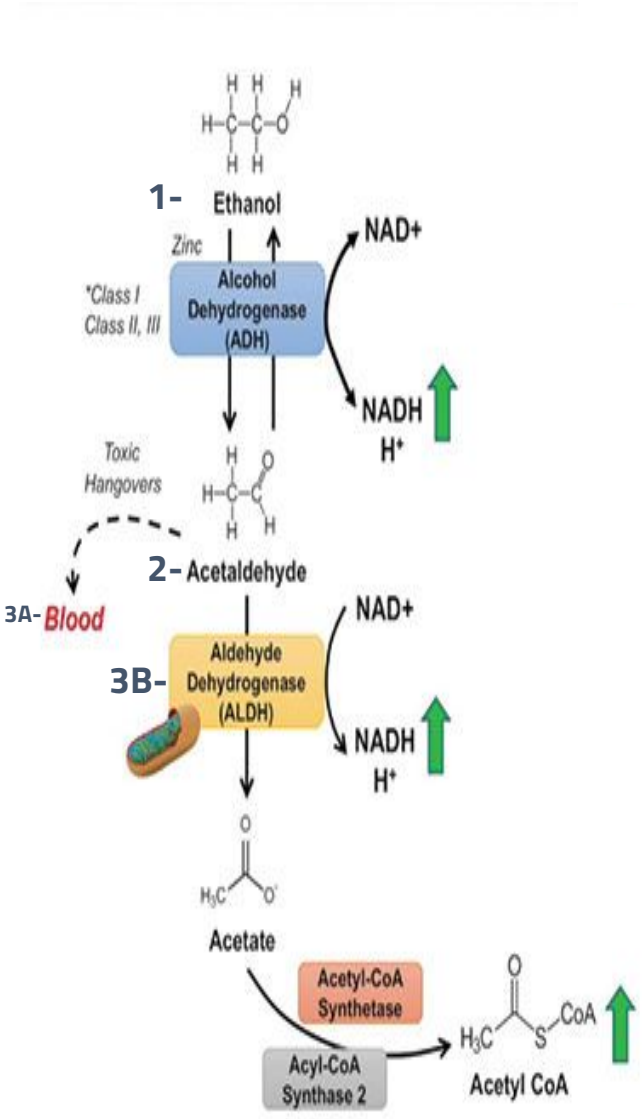
***Girls' slides only**

Hepatic Ethanol Metabolism*



Extra Explanation

(or you can watch the video)



Major Pathway:

1- The metabolism of ethanol begins with the enzyme ADH which processes ethanol into acetaldehyde (NAD+ is reduced to NADH).

2- Acetaldehyde is very toxic. It's actually associated with the hangover symptoms that people experience after ingesting ethanol.

3A- acetaldehyde can leave the liver, enter the bloodstream, and have other toxic effects on other tissues.

3B- It's very important for the liver to get rid of acetaldehyde by using another enzyme, **aldehyde dehydrogenase**. This enzyme is located in the mitochondria. It metabolizes acetaldehyde into acetate (NAD+ is reduced into NADH). Note that the aldehyde dehydrogenase reaction is irreversible unlike the alcohol dehydrogenase reaction. As acetate increases, acetyl-CoA increases too.

Minor Pathway (Microsomal Oxidation):

A- In the smooth endoplasmic reticulum:

It occurs in the liver by the enzyme CYP2E1 which is a **CYP450** enzyme. This enzyme will process ethanol into acetaldehyde. We know that most of the metabolism of alcohol occurs by alcohol dehydrogenase; however, when ethanol concentrations are very high, this enzyme becomes important in removing the excess ethanol.

B- In the mitochondria:

The majority of the produced acetaldehyde will be converted into acetate by **acetaldehyde dehydrogenase**

Genetic Variation of Alcohol Metabolism

Aldehyde dehydrogenase polymorphism[1]

- **Asian** populations (Including Chinese, Japanese, Taiwanese, Korean) have genetic variation in **aldehyde dehydrogenase** resulting in a variant allele (ALDH2*2 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.) 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

- 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[2]) i.e. rate of elimination is the same at low and high concentration have high risk of toxicity

Alcohol Mechanism of Action

Alcohol is a CNS depressant

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

1) existence of one gene in different forms
2) Constant amount which means increasing the conc. Will not affect its excretion e.g. Aspirin, Phenytoin, Constant amount is lost per unit time, the rate of excretion is independent of the con. of it in plasma
3) Increase number of NMDA receptors → increases glutamate effect

Acute[1] Actions of Alcohol

A) In mild-moderate amounts

CNS depression:
- Relieves anxiety, euphoria (feeling of well-being) only initially
- 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

B) In severe amounts (common suicide method in alcoholics)

Severe CNS depression ● Respiratory depression ● Respiratory acidosis ● Pulmonary Aspiration ● Nausea, vomiting, aspiration of vomitus ● CVS depression ● Volume depletion ● **Hypotension**[2] ● Hypothermia ● Coma, death

Chronic Actions of Alcohol

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

Tolerance[3]	Dependence	Addiction	Behavioral Changes

Liver
1. Hepatic cirrhosis
2. Liver Failure

Paracetamol is considered dangerous for alcoholics

CVS
1. Hypertension (due to damage of endo. lining)
2. Myocardial infarction

Hematological disorders
Neoplasia

GIT
1. Irritation.
2. Inflammation.
3. Bleeding
4. Nutritional deficiencies

CNS
1. Cerebral atrophy
2. Cerebellar degeneration
3. Peripheral neuropathy
4. Wernicke encephalopathy or Korsakoff IRREVERSIBLE psychosis may occur

Endocrine
1. Gynecomastia
2. Testicular atrophy

1) One time administration
2) CNS and vasomotor depression→ vasodilation and bradycardia →Hypotension
3) With repeated use they have a reduced response to alcohol, an increased dose is needed to achieve the needed response

Complications of Chronic Alcohol Use (Alcoholism)

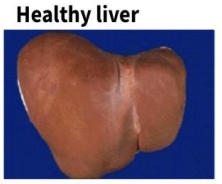
Liver

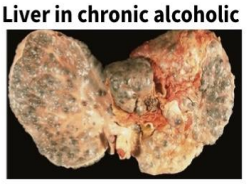
The **most common & important** medical complication occurs with liver:

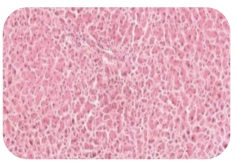
- Reduction of gluconeogenesis (decrease glucose conc.) → Hypoglycemia
- **Fatty liver/ alcoholic steatosis** due to fat accumulation
- Hepatitis
- **Hepatic cirrhosis**: jaundice, Ascites, bleeding, encephalopathy.
- Irreversible liver failure.

Acetaldehyde is more toxic than alcohol causing inflammation and fat cell proliferation.
Click here to view related pathway

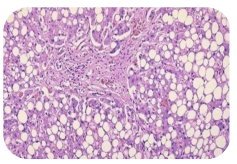
Acetate → Acetyl CoA → Fatty acid synthesis → Fatty liver







Healthy Liver



Fatty Liver

Alcoholic Liver Disease: Normal Liver ⇆ Steatosis ⇆ Steatohepatitis → (irreversible) Cirrhosis

GIT

- Direct toxic action on epithelium causes : Gastritis, hemorrhagic esophagitis, ulcer diseases, pancreatitis GIT
- Diarrhea
- Deficiency of vitamins.
- 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**
- Cardiac hypertrophy
- Congestive heart failure.
- **Arrhythmia** due to K^+ and Mg^{2+} depletion
- **Hypertension**[1] due to increased Ca^{2+} & sympathetic activity **and destruction to endothelium**

1) Acetaldehyde causes Vasodilation (acute effect) but chronic use causes chronic Vasodilation which lead to response by RAAS and other compensatory mechanism causing Hypertension.

Complications of Chronic Alcohol Use (Alcoholism)

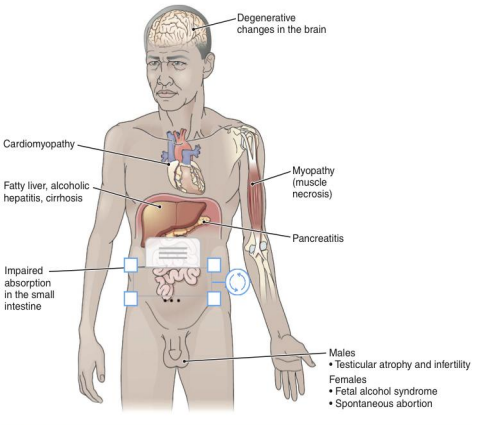


Figure 48.11
The effects of chronic alcohol abuse.

Hematological

- **Iron deficiency anemia** (due to inadequate dietary intake & GIT bleeding).
- **Megaloblastic anemia**: (due to folate deficiency, malnutrition, impaired folate absorption).
- **Hemolytic anemia** rupture of RBCs by free radical
- Bone marrow suppression
- **Thrombocytopenia** (suppressing platelet formation, **prolong bleeding times**[1]).
- Impaired production of vitamin-K dependent clotting factors leading to prolonged prothrombin time.

1) prolonged bleeding time is due to both effects of:
- ➢ suppressing platelet formation
- ➢ Impaired production of vitamin-K dependent clotting factors

Endocrine

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

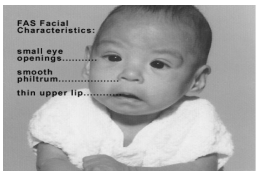
CNS

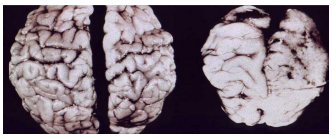
- Tolerance
- Physiological and psychological dependence
- Addiction: **dopamine, serotonin and opioids** are involved only initially, involved in reward.
- Neurologic disturbances
- Wernicke-Korsakoff syndrome

Chronic Alcoholism Associated Syndromes

1 Fetal alcohol syndrome (FAS)

FAS: Facial malformation. Attention deficit disorder. Septal defects, low I.Q





- Irreversible
- Ethanol rapidly crosses placenta and the fetal blood brain barrier

Prenatal exposure to alcohol causes:

1. Intrauterine growth retardation (due to hypoxia)
2. Congenital malformation (teratogenesis):

- Congenital heart defects
- Physical and mental retardation.[1]
- Microcephaly most dangerous
- Impaired facial development

It's so dangerous and that's why there's **no safe** level of alcohol during pregnancy

2 Wernicke-korsakoff syndrome

It is a combined manifestation of two disorders:

Wernicke's encephalopathy **Acute, reversible**	characterized by: 3 main symptoms • **C**hanges in mental state as **c**onfusion,delirium • **O**cular disturbances (Nystagmus or ophthalmoplegia) • **A**taxia, unsteady gait • **T**hiamine deficiency
Korsakoff's psychosis **Chronic, IRREVERSIBLE**	• Targets the limbic system • Impaired memory (anterograde & retrograde amnesia) • Cognitive & Behavioral dysfunction. • very severe, might cause death, needs urgent treatment

Causes thiamine (vitamin B1) deficiency due to:

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

Treated by: thiamine + dextrose (to correct hypoglycemia) -containing IV fluids. & stopping alcohol use

3 Alcoholism Tolerance

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

Alcohol causes upregulation of its own metabolism

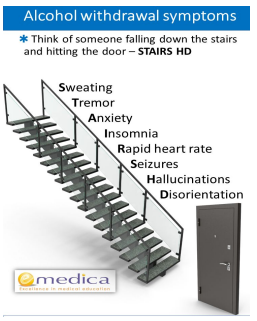
Metabolic tolerance (Pharmacokinetic)	due to induction of **liver microsomal enzymes e.g.CYP450**
Functional tolerance (Pharmacodynamic)	due to **change in CNS sensitivity**[2] This occur when they show few obvious signs of intoxication even at high blood alcohol concentration

1) Babies can experience withdrawal and cravings.also, they will have a lower IQ and Impared memory. Later in life they are likely to develop anxiety due to failure of coping with life stresses
2) Down regulation of GABA and up regulation of Glutamate

Alcoholism Withdrawal Symptoms

All these symptoms are due to super-sensitivity of glutamate receptors & Hypo-activity of GABA receptors are possibly involved. Reverse the suppression effects

- Autonomic hyperactivity & craving for alcohol
- Vomiting, thirst
- Profuse sweating, severe tachycardia
- Vasodilatation, fever
- Grand mal **seizures** (after 7-48 hr alcohol cessation).
- Delirium, tremors, anxiety, agitation, insomnia
- Transient visual/ auditory illusions, violent behavior, hallucinations.



Management of alcoholism withdrawal

Substituting alcohol with a long-acting sedative/hypnotic drug then tapering (gradually decreasing) the dose.

Benzodiazepines

- **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.

Acamprosate

weak NMDA receptor antagonist & GABA activator (weakly mimics alcohol effect but is not addictive) → reduce psychic craving

Clonidine & Propranolol

inhibits the action of exaggerated sympathetic activity

Fluoxetine

(SSRI, anxiolytic)

Increases serotonin (Antidepressant). Helps because in addiction serotonin and dopamine are reduced causing depression (Not used for acute control)

To Prevent Alcohol Relapse:

Disulfiram therapy 250 mg daily

Disulfiram: induced symptoms render alcoholic afraid from drinking alcohol

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

Click here to view related pathway

Alcohol is converted to Acetaldehyde which is then broken down By Acetaldehyde dehydrogenase, when Acetaldehyde dehydrogenase is inhibited → Acetaldehyde levels build up causes the effect of "hangover" to happen which decreases the likelihood that a person will drink alcohol again

Acetaldehyde produces extreme discomfort vomiting, diarrhea, flushing, hotness, cyanosis, tachycardia, dyspnea, palpitations & headache. Similar to polymorphism in asian population

Alcohol and drug interactions

Acute Alcohol use	causes inhibition of liver enzyme, → decreases metabolism of some drugs and increases their toxicities e.g. bleeding with warfarin
Chronic Alcohol use	induces liver microsomal enzymes → increases metabolism of drugs such as warfarin, propranolol ... etc

1. **Acetaminophen** (panadol) + 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** (NSAIDs inhibit platelet aggregation and alcohol suppress platelet formation and vitamin-k dependent clotting factors)

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.**

MCQs

Q1: A 45-year-old man who has been injured in a car accident is brought into the emergency department. His blood alcohol level at admission is 275 mg/ dL. Hospital records show a prior hospitalization for alcohol-related seizures. His wife confirms that he has been drinking heavily for 3 weeks. What treatment should be provided to the patient if he goes into withdrawal?			
A- No pharmacological treatment is necessary	B-Lorazepam	C-Phenytoin	D-Buspirone
Q2: which of the following statements is correct about acute alcohol use?			
A- inhibits CYP450 2E1	B- induces CYP450 2E1	C-No effect on CYP450 2E1	D- increases metabolism of warfarin
Q3: Wernicke-Korsakoff Syndrome is action of chronic alcohol use on?			
A- CNS	B-CVS	C-Endocrine	D-GIT
Q4: which of the following is a mechanism of action of chronic alcohol use?			
A- Up-regulation of NMDA receptors	B-Down regulation of GABA	C-Inhibition of glutamate action on NMDA receptors	D-both A and B
Q5: Alcohol excretion			
A- zero-order kinetic	B-first order kinetics	C- conc.-dependent	D-A and C
Q6: Which of the following agents is an inhibitor of aldehyde dehydrogenase?			
A- Ethanol	B-Naltrexone	C-Disulfiram	D- Fomepizole
Q7: The symptoms resulting from the combination of disulfiram and alcohol are:			
A- acute psychotic reaction	B-Nausea, vomiting	C-Hypertensive crisis	D-Respiratory depression and seizures
Q8: The most common medical complication of alcohol abuse is:			
A- Liver failure including liver cirrhosis	B-Tolerance and physical dependence	C-Hypoglycemia	D-All of them
Q9: An alcoholic male has developed hepatic cirrhosis.To control the ascites and edema, which should be prescribed remember #cardiorenal?			
A- Acetazolamide	B-Chlorthalidone	C-Furosemide	D-Spironolactone

1	2	3	4	5	6	7	8
B	A	A	D	A	C	B	D

SAQ

Q1) list four actions of chronic alcohol use?

Q2) what is the mechanism of action of acute alcohol use?

Q3) list some example of acute action of alcohol use on CNS and CVS in mild to moderate amount

Q4) list the management approaches of alcohol withdrawal syndrome

Q5) mention three drugs that might interact with alcohol ?

Q6) A 24-year-old pregnant woman has a long history of alcohol abuse. What is the effect of that on the fetus?

Answers

A1) Dependence, addiction, behavioral changes, tolerance

A2) 1- Enhancement of the effect of GABA on its GABA receptors in brain leading to CNS depression.

2- Inhibition of glutamate action on NMDA receptors leading to disruption in memory, consciousness, and alertness.

A3) CVS: Myocardial contractility depression, Vasodilatation. CNS: Relieves anxiety, euphoria, sedation, hypnosis

A4) Substituting alcohol with a long-acting sedative/hypnotic drug then tapering the dose. (Benzodiazepines, acamprosate, Clonidine & Propranolol, Fluoxetine)

A5) Acetaminophen, NSAIDs ,Narcotic drugs (Codeine, methadone)

A6) Fetal alcohol syndrome which is associated with: Intrauterine growth retardation (due to hypoxia), Congenital malformation (teratogenesis)

Feedback Form

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