King Saud University

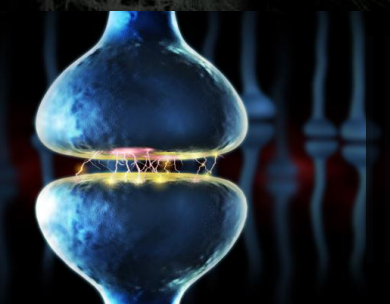
College of Medicine

2nd Year, 1st Block

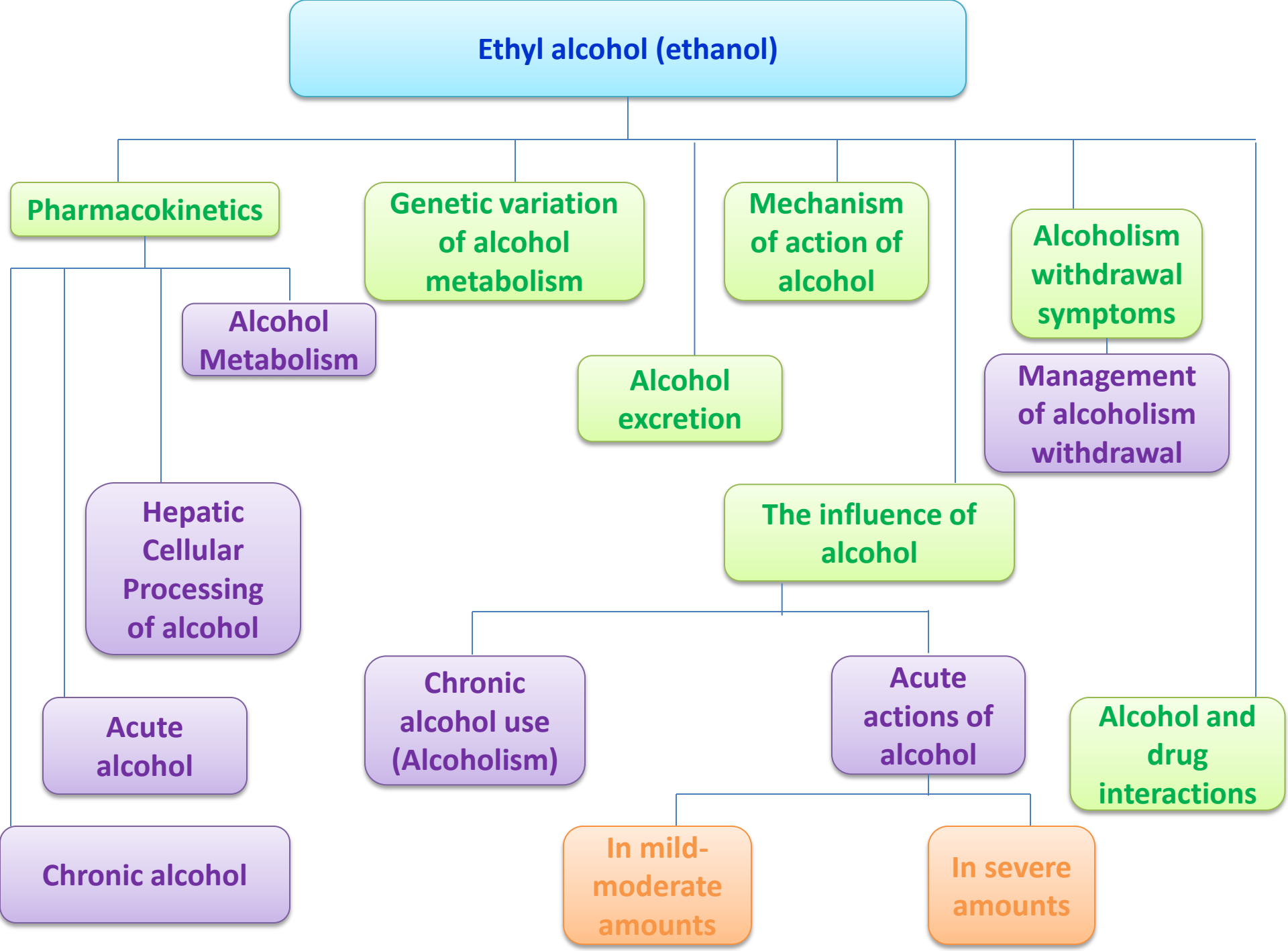
PHARMACOLOGY 433

MED 433 Teams

L13: Alcohol and the brain



CNS Block


Ethyl alcohol (ethanol)
Pharmacokinetics
Genetic variation of alcohol metabolism
Mechanism of action of alcohol
Alcoholism withdrawal symptoms
Alcohol Metabolism
Alcohol excretion
Management of alcoholism withdrawal
Hepatic Cellular Processing of alcohol
The influence of alcohol
Chronic alcohol use (Alcoholism)
Acute actions of alcohol
Alcohol and drug interactions
Acute alcohol
Chronic alcohol
In mild-moderate amounts
In severe amounts

Ethyl alcohol (ethanol):

Ethyl alcohol (ethanol) is the most commonly abused drug in the world.

Pharmacokinetics

- **lipophilic**
- It crosses **all biological membranes** & completely absorbed from GIT.
  "Crosses placenta and excreted in milk "*
- distributed to all body tissues
  "Volume of distribution = Total body water "

Metabolism in gastric mucosa & liver

- **Oxidation of ethanol** —(alcohol dehydrogenase)→ **acetaldehyde**

  —(*Aldehyde dehydrogenase*; *cyt-p450 (CYP2E1)*)→ **acetate** + reduces NAD^{+}* to NADH.

  Acetate → **CO2 + water.**

1- Oxidation is : remove H so, the name of enzyme for oxidation is **dehydrogenase**
2- Oxidation done by 2 type of enzymes: ***1-Non-microsomal enzyme*** (in mitochondria and cytosol) ***2- hepatic microsomal enzyme mainly cyt-p450 (CYP2E1)*** in liver.
3- we need co-enzyme which is NAD to take the H that dehydrogenase remove it.

**It causes Irreversible fetal alcohol syndrome:*

Intrauterine growth retardation (due to hypoxia)
-Congenital malformation (Teratogenesis):

-Microcephaly
-Impaired facial development
-Congenital heart defect
-Physical & mental retardation.

❖ **Low ethanol conc., > *minor metabolism* by MEOS (microsomal ethanol-oxidizing system) CYP450 "CYP2E1"**

❖ **Continuous alcohol use > enzyme is stimulated > alcohol metabolism & tolerance*.**

N.B\ (Acetaldehyde) more toxic than alcohol

alcohol

Pharmacokinetics

Acute *alcohol consumption

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

*Acute : Only once, the patient not addicted.

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)

Alcohol excretion:

- Excreted unchanged in urine (2-8%).
- Excretion unchanged via lung (basis for breath alcohol test*). *It is a test to asses alcohol amount in the body, It usually used to drivers
- Rate of elimination is zero-order kinetic (not concentration-dependent) i.e. rate of elimination is the same at low and high concentration.(So we have to be careful to high dose or it will cause a toxic effect)

Mechanism of action of alcohol: Is a CNS depressants

Acute alcohol causes:

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 channels (Ca influx to nerve cells) leading to alcohol tolerance & withdrawal symptoms (tremors, exaggerated response & seizures).

Genetic variation of alcohol metabolism

Aldehyde Dehydrogenase polymorphism

- Asian populations have genetic variation in aldehyde dehydrogenase. (acetaldehyde will not be converted 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. *can use this as treatment, see later*

Acute actions of alcohol

In mild-moderate amounts	In severe amounts
CNS depression 1. relieves anxiety, euphoria (feeling of well-being). 2. Nystagmus, slurred speech, impaired judgment, ataxia 3. Sedation, hypnosis, loss of consciousness	1. Severe CNS depression 2. Nausea, vomiting, aspiration of vomitus. 3. Respiratory depression. 4. CVS depression 5. Hypovolemia 6. Hypotension 7. Hypothermia 8. Coma, death.
CVS depression 1. Myocardial contractility depression 2. Vasodilatation due to vasomotor center depression & direct smooth muscle relaxation caused by acetaldehyde.	

Chronic ethanol abuse (alcoholism) is associated with many complications

Liver	Gastrointestinal system	Cardiovascular System
• Reduction of gluconeogenesis. • Fatty liver/ alcoholic steatosis • Hepatitis • Hepatic cirrhosis: jaundice, ascites, bleeding, encephalopathy. • Irreversible liver failure. Acetaldehyde is more toxic than alcohol →causing inflammation and fat cell proliferation	• Gastritis, hemorrhagic esopahgitis, ulcer diseases, pancreatitis (due to direct toxic action on epithelium) • Diarrhea • Deficiency of vitamins. • Exacerbates nutritional deficiencies • weight loss, and malnutrition.	• 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.

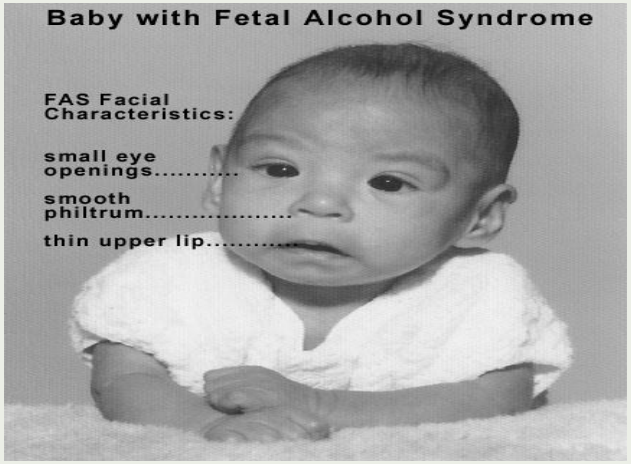
Chronic ethanol abuse (alcoholism) is associated with many complications

Hematological	Endocrine	CNS
• 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.	• Hypogonadism: 1- In women: ovarian dysfunction, amenorrhea, anovulation, hyperprolactinemia, infertility. 2- 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.	• Tolerance • Physiological and psychological dependence • Addiction: dopamine, serotonin and opioids are involved. • Neurologic disturbances • Wernicke-Korsakoff syndrome

Chronic ethanol abuse (alcoholism) is associated with many complications

Fetal Alcohol Syndrome

- **Irreversible**
- **Ethanol rapidly <u>crosses placenta</u>**
- **Pre-natal exposure to alcohol causes:**
- **- Intrauterine growth retardation (due to hypoxia)**
- **Congenital malformation (teratogenesis):**
  1. **Microcephaly (small head)**
  2. **Impaired facial development**
  3. **Congenital heart defects**
  4. **Physical and mental retardation**



Wernicke-Korsakoff syndrome

- **It is a combined manifestation of 2 disorders:**

1) Wernicke's encephalopathy: characterized by
ocular disturbances - unsteady gait
changes in mental state as confusion, delirium, ataxia

2) Korsakoff's psychosis:
impaired memory & cognitive and behavioral dysfunction.

- **Cause: thiamine (vitamin B1) deficiency**
- **Treated by: thiamine + dextrose-containing IV fluids.**

Alcoholism Tolerance

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

1) Metabolic tolerance (pharmacokinetic): due to induction of liver microsomal enzymes.

2) Functional tolerance (Pharmacodynamic): due to change in CNS sensitivity.

Alcoholism withdrawal symptoms & it's mangement

Alcoholism withdrawal symptoms (Autonomic hyperactivity due to super-sensitivity of glutamate receptors & hypoactivity of GABA receptors)	Management of alcoholism withdrawal symptoms Substituting alcohol with a long-acting sedative hypnotic drug then tapering the dose.
craving for alcohol	Benzodiazepines as (chlordiazepoxide, diazepam) or lorazepam that is preferable (shorter duration of action).
Vomiting, thirst	Fluoxetine
Profuse sweating, severe tachycardia	Clonidine & Propranolol: inhibits the action of exaggerated sympathetic activity
Vasodilatation, fever	Acamprosate a weak NMDA receptor antagonist & GABA activator, reduce psychic craving.
Delirium, tremors, anxiety, agitation, insomnia, hallucinations.	To prevent alcohol relapse:
Grand mal seizures (after 7-48 hr alcohol cessation) Due to super-sensitivity of glutamate receptors & hypoactivity of GABA receptors are possibly involved.	Disulfiram therapy: Inhibits hepatic aldehyde dehydrogenase, this will increase blood level of acetaldehyde. (As in Asian population) Acetaldehyde produces extreme discomfort, vomiting, flushing, tachycardia, dyspnea, palpitations & headache. Disulfiram-induced symptoms render alcoholics afraid from drinking alc

Alcohol and drug interactions

Acute alcohol use	• 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.	e.g. warfarin, propranolol
Acetaminophen + alcohol (chronic use)	➢ risk of hepatotoxicity.	
NSAIDs + alcohol	➢ Increase in the risk of developing a major GI bleed or an ulcer.	
Alcohol suppresses gluconeogenesis > may increase risk for Hypoglycemia in diabetic patients.		
Narcotic drugs (codeine and methadone) + alcohol	➢ risk of respiratory and CNS depression.	

Summary

- Alcohol Lipophilic > rapid and easily absorbed > large V.D (distribute in all body).
- Most of alcohol metabolized in the liver.
- At low ethanol conc.(Acute alcohol),most of alcohol metabolism by alcohol dehydrogenase and 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.
- Acetaldehyde in more toxic than ethanol
- Asian populations have low Aldehyde Dehydrogenase >> metabolized alcohol at slower rate >> develop "Acute acetaldehyde toxicity"
- Rate of elimination is zero-order kinetic (not concentration-dependent) i.e. rate of elimination is the same at low and high concentration.
- Alcohol suppresses gluconeogenesis, which may increase risk for hypoglycemia in diabetic patients.
- Acute acetaldehyde toxicity : vomiting, vasodilatation, flushing
- Withdrawal symptoms: hypersensitivity, Autonomic hyperactivity, tremors, hallucinations, exaggerated response & seizures.
- Hepatic cirrhosis: jaundice, ascites, bleeding, encephalopathy.
- Fetal Alcohol Syndrome (FAS) : Microcephaly , Impaired facial development ,Congenital heart defects , Physical and mental retardation.
- Wernicke's encephalopathy: ocular disturbances - unsteady gait, changes in mental state as confusion, delirium, ataxia
- Korsakoff's psychosis: impaired memory & cognitive and behavioral dysfunction.

Summary of drugs

- **Alcohol and drug interactions**

1- warfarin + Acute alcohol = cause Bleeding

2- Phenytoin + Acute alcohol = toxicity

3- warfarin + Chronic alcohol = cause Drug interactions

4- Propranolol + Chronic alcohol = cause Drug interactions

5-Acetaminophen + alcohol (chronic use) = risk of hepatotoxicity. Alcohol can also increase the conversion of acetaminophen to toxic metabolites in liver

6- NSAIDs + alcohol = Increase in the risk of developing a major GI bleed or an ulcer.

7- Narcotic drugs (codeine and methahdone) + alcohol= risk of respiratory and CNS depression.

- **Treatment of Wernicke-Korsakoff syndrome : 8- Thiamine + dextrose-containing IV fluids.**
- **Management of alcoholism withdrawal :**

9-IV/ po Benzodiazepines as (chlordiazepoxide, diazepam) or lorazepam that is preferable (shorter duration of action): prevent irritability, insomnia, agitation & seizures. Avoid excessive dose that causes respiratory depression & hypotension.

10- Fluoxetine

11- Clonidine & Propranolol: inhibits the action of exaggerated sympathetic activity

12- Acamprosate: a weak NMDA receptor antagonist & GABA activator, reduce psychic craving.

- **To prevent alcohol relapse:**

13- Disulfiram therapy: 250 mg daily, blocks hepatic aldehyde dehydrogenase, this will increase blood level of acetaldehyde.

Alcohol : is a CNS depressants

	Pharmacokinetics of ethanol	Mechanism of action of alcohol	Actions of alcohol:
Acute alcohol (Enzyme Inhibitor)	**inhibits CYP450 2E1** warfarin, phenytoin +Acute alcohol = decrease metabolism of alcohol and the drugs, increases their **toxicities** e.g. **bleeding** with warfarin	• **Enhancement of GABA** >> CNS depression • **Inhibition of glutamate** on NMDA receptors >> disruption in memory, consciousness, alertness	**Every thing go down** **In mild-moderate amounts** • CNS depression(e.g: euphoria, loss of consciousness) • CVS depression(e.g: **Vasodilatation caused by acetaldehyde)** **In severe amounts** • Severe CNS depression (e.g:respiratory depression, coma.) • CVS depression • **Hypotension** • Coma, death.
Chronic alcohol (Enzyme Inducer)	**induces liver microsomal enzyme CYP450 2E1** warfarin, propranolol + chronic alcohol = significant increases in ethanol metabolism **(Tolerance)** & metabolism of other drugs as warfarin **(Drug interactions).**	**up-regulation of NMDA receptors & Ca influx to nerve cells** >> tolerance & withdrawal symptoms	▪**Tolerance, dependence, addiction, behavioral changes** ▪**Liver:** hepatic cirrhosis & liver failure. ▪**CVS: hypertension**, myocardial infarction ▪**CNS: cerebral atrophy,** cerebellar degeneration, and peripheral neuropathy. **Wernicke encephalopathy or Korsakoff psychosis** may occur. ▪**GIT system: irritation,** inflammation, **infections,** bleeding, **Deficiency of vitamin** s ,nutritional deficiencies ▪**Endocrine system:** gynecomastia & testicular atrophy ▪**Hematological disorders** (all kinds of anemia), neoplasia.

Quiz yourself

Q1: Asian man drink alcohol and come to you Suffers from vomiting, vasodilatation, flushing in his face what is the cause of his symptoms?

A) Korsakoff's psychosis:
B) Acute acetaldehyde toxicity
C) Hepatic cirrhosis
D) Fetal Alcohol Syndrome

Q2: If you have diabetic and alcohol adducted patient , what you should recommend to him?

A) Decrease the dose of Antidiabetic drug
B) increase the dose of Antidiabetic drug
C) Stop the Antidiabetic drug
D) There is no difference

Q3:Which of the following metabolic alterations may be associated with chronic alcohol abuse?

A) Hyperglycemia
B) Increased serum concentration of phosphate
C) Severe loss of potassium and magnesium
D) Decreased serum concentration of sodium

Q4: Which of the following agents is an inhibitor of aldehyde dehydrogenase?

A) Fomepizole
B) Ethanol
C) Disulfiram
D) Naltrexone

Q5: What kind of deficiency developed in chronic alcoholics? :

A) Folate deficiency
B) Iron deficiency
C) Vit-B12 deficiency
D) A & B

Q6: Alcohol diminish the production of which vitamin? :

A) Vit-C
B) Vit-B12
C) Vit-K
D) Vitamin A deficiency

Q7: We have an alcoholic patient with a family history of alcohol abuse, what's the best drug to reduce his drinking habits?

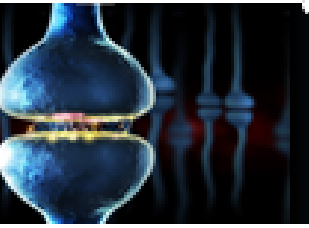
A) Fluoxetine
B) Clonidine
C) Propranolol
D) All above

Q8: Wernicke-Korsakoff syndrome develops due to which deficiency? :

A) Iron Deficiency
B) Thiamin Deficiency
C) Vit-B12 deficiency
D) Vitamin A deficiency

Answers:

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



CNS Block

PHARMACOLOGY 433

THIS WORK WAS DONE BY :

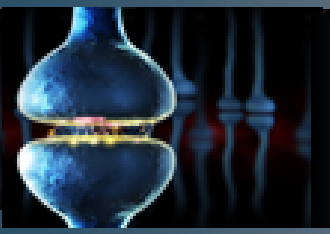
Raneem Alotaibi	Ahmed Aldakhil
Awatif alenazi	
Hanan Aldossari	
Jumanah Albeeybe	
Noura Alrayes	
Nada Bin dawood	

Contact us for any questions or comments :

Pharma_433@yahoo.com

@pharma_433

We hope that we made this lecture easier for you
Good Luck !



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