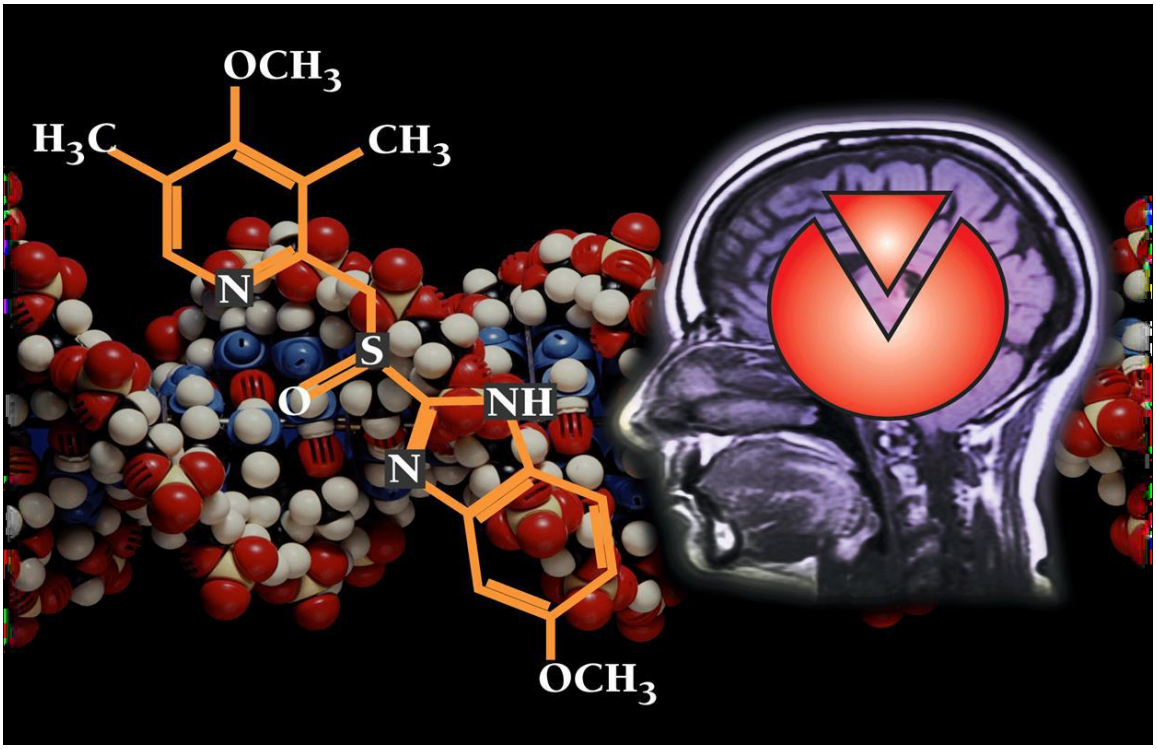
King Saud University
College Of Medicine
Pharmacology Team 430
CNS Block

Alcohol & The brain



Note: notes in light blue margins are just for explanation

Done By:

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- Today, alcohol primarily in the form of ethyl alcohol **(ethanol)** is widely consumed
- It is the most commonly abused drug in world.
- Alcohol, like other sedative/ hypnotic drugs ،in low-moderate amounts relieves anxiety & fosters a feeling of well-being/ euphoria.

Pharmacokinetics:

- water-miscible molecule, **completely absorbed from GIT**
- Peak blood ethanol concentration after **po(Oral)** doses: **30 -75 min, absorption is delayed by food .**
- Volume of distribution = Total Body Water.
- **Over 90% of alcohol consumed is oxidized in the liver**

Note: For an equivalent oral dose of alcohol, women have a higher peak concentration than men (because women have lower total body water content.) In the central nervous system, the concentration of ethanol rises quickly since the brain receives a large proportion of total blood flow and ethanol readily crosses biologic membranes. (Cross BBB)

Metabolism (in gastric mucosa & liver):

1- Oxidation of ethanol to acetaldehyde via

A- **ADH**; reduction of **NAD^+ to NADH**. ***Mainly in liver***.

B- Microsomal **ethanol oxidizing system**

Note:
-ADH; Alcohol dehydrogenase
-ALDH; Aldehyde dehydrogenase . -
NAD^+/NADH: nicotinamide adenine dinucleotide

2- Acetaldehyde is converted to acetate via AlDH, which also reduce NAD^+ to NADH. (Acetate ultimately is converted to CO_2 + water.**)**

Over 90% of alcohol consumed is oxidized in the liver; much of the remainder is excreted through the lungs and in the urine.

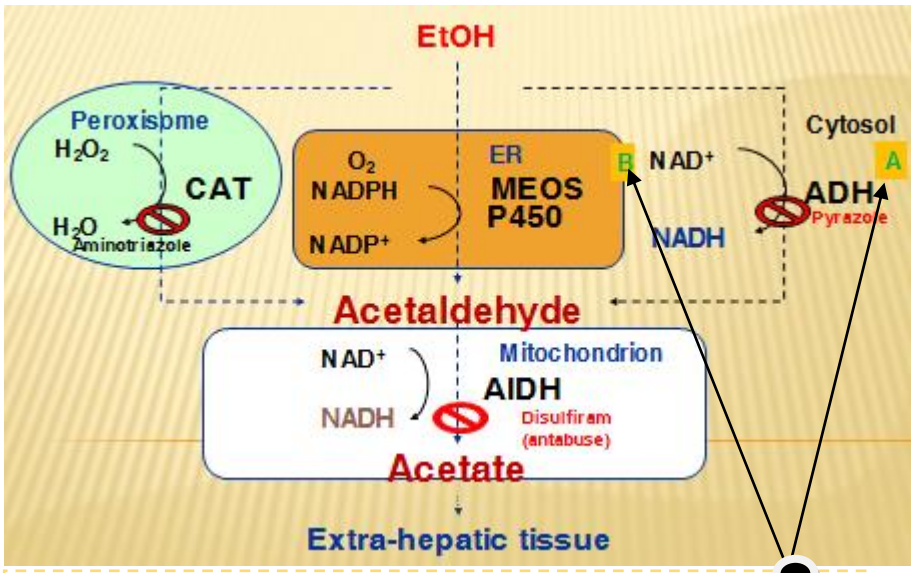
ADH ALDH
CH3CH2OH →→ CH3CHO→→CH3COOH
Ethanol Acetaldehyde Acetic Acid

Note: The excretion of a small but consistent proportion of alcohol by the lungs is utilized for breath alcohol tests that serve as a basis for a legal definition of "driving under the influence" in many countries.

Hepatic Cellular Processing of EtOH(Ethanol)

Process occurs in three systems
-ADH: alcohol dehydrogenase 80% of processing
-CAT: catalase; ~5% of processing
-MEOS: microsomal ethanol-oxidizing system; ~15% of processing

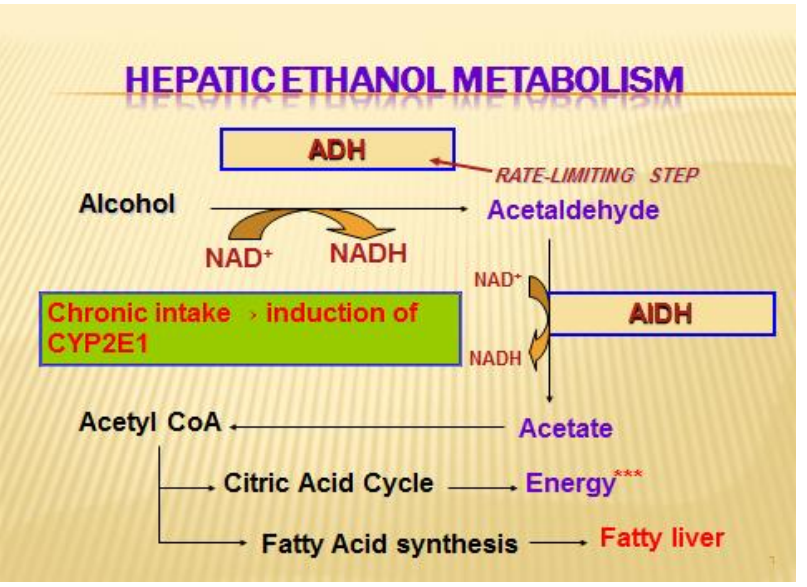
Abbreviations:
- **$NADP^+$/NADPH**: nicotinamide adenine dinucleotide phosphate
- **AlDH**: aldehyde dehydrogenase.
- **ADH:** Alc dehydrogenase
- **MEOS**: Microsomal ethanol-oxidizing system
- **P450**: cytochrome P450



Note: Metabolism of ethanol by two main processes (A&B) **alcohol dehydrogenase and the microsomal ethanol-oxidizing system (MEOS).** Aldehyde dehydrogenase is inhibited by **disulfiram.**

Note: when large amounts of ethanol are consumed**, the alcohol dehydrogenase system(ADH)** becomes saturated owing to depletion of the required cofactor**, NAD$^+$.** As the concentration of ethanol increases above 100 mg/dL, there is increased contribution from the **MEOS** system, which does not rely upon **NAD$^+$ as a cofactor**.

Note: During chronic alcohol consumption, **MEOS** activity is induced. As a result, chronic alcohol consumption results in significant increases not only in ethanol metabolism but also in the clearance of other drugs **eliminated by the cytochrome P450s** that constitute the **MEOS system and** the generation of the toxic byproducts of cytochrome P450 reactions (toxins, free radicals, H_2O_2).



Effects of Alcohol

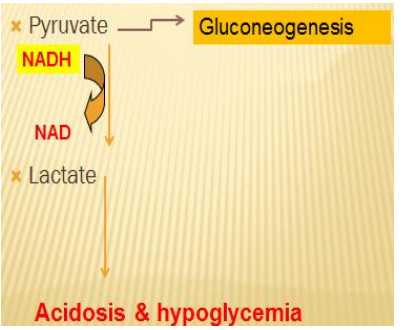
Chronic Ethanol consumption:

1- Induces **cytochrome P450,** leads to generation of **ROS**(reactiove oxygen species) **& RNS**(reactive nitrogen species) + hypoxia.
2- Decrease **NAD & increase NADH** by Liver.
3- Accumulation **of acetaldehyde**. (Associated with the 'flushing reaction' immediately following alcohol intake ,due to increased acetaldehyde in some individuals)

Note: Chronic use decreases the amounts of NAD, which is need as a cofactor to oxidize **acetaldehyde** along with the help of the enzyme AIDH.

These 3 biochemical changes contribute to:

- DNA damage, hepatocyte injury & liver disease.
- **Pyruvate** is reduced to **lactate** to **generate NAD**, and to dispose excess **NADH** ; causing **acidosis & hypoglycemia** in **malnourished alcoholics** (Ethanol does not have any minerals, vitamins, CHs, fats \ protein). (pyruvate is needed for gluconeogenesis)
- Lactate inhibits uric acid excretion;**hyperuricemia.**
- Anemia
- Cardiomyopathy; **arrhythmia & HTN.**
- **Liver failure & death within 10 yrs.**



Note: Liver disease is the most common medical complication of alcohol abuse; an estimated 15–30% of chronic heavy drinkers eventually develop severe liver disease. Alcoholic fatty liver, a reversible condition, may progress to alcoholic hepatitis and finally to cirrhosis and liver failure.

Other effects:

- Chronic alcohol abuse can lead to **alcohol intrauterine growth retardation (**refers to the poor growth of a baby while in the mother's womb during pregnancy)**, congenital malformation & teratogenicity.**
- **Gastritis & ulcer diseases**
- **Cancer (tongue, mouth, oropharynx, esophagus, liver, & breast).**
- **Pancreatitis.**

Effects of alcohol greatly depends on dose and frequency of use.

In order of increasing dose (or number of drinks),alcohol is anxiolytic ⇨ mood-enhancing ⇨ sedative ⇨ slows reaction time ⇨ produces motor incoordination ⇨ impairs judgment (making it dangerous and illegal to drive a car).

At very high doses alcohol produces loss of consciousness

Medical complications of chronic alcoholism:

- **Liver disease**: most common medical complication. **Accumulated acetaldehyde**: hepatotoxicity.
- **Fatty liver/ alcoholic steatosis** (common, reversible, hepatomegaly, slight elevation in liver enzyme)
- Followed by:**hepatic cirrhosis** (jaundice, ascites, bleeding & encephalopathy) &
- liver failure & death within 10 yrs.

2-Acute Ethanol intoxication:

- **CNS depression**: sedation, relief anxiety, **higher conc**.: slurred speech, ataxia, & impaired judgment
- **Respiratory depression** leading to **respiratory acidosis & coma**
- **Death** can occur from respiratory depression + aspiration of vomitus.
- Significant depression of myocardial contractility
- **Vasodilatation** due to depression of vasomotor center & direct smooth muscle relaxation caused by acetaldehyde.
- **Volume depletion, hypothermia & Hypotension**
- **Hypoglycemia** due to reduced Carbohydrates intake & malnourished alcoholics.(Pyruvate compensations of consumed NAD& excess NADH)

Management:

Supportive therapy till metabolism clear body to low levels

- Hypotension/hypovolumia → **IV fluids**
- **Artificial respiration**
- Hypoglycmia:**IV gluc**
- Coma: lavage, **naloxone**

Note: Table is not important

Intoxication	Ethanol level
Mild signs	<500 mg/L (0.05%)
Frequent Psychomotor Impairment	≤ 1000 mg/L (0.1%)
Psychomotor Impairment in everyone	1500 mg/L(0.15%)
anesthesia & coma	2500 mg/L (0.25%)
Death (respiratory depression)	5000 mg/L (0.5%)

Elevated acetaldehyde during Etol intoxication

- Nausea & headache
- Sensitivity reactions, VD & facial flushing
- Increase skin temperature.
- Lower BP
- Sensation of dry mouth & throat
- **Bronchoconstriction** & allergic-type reactions
- **Euphoric effects** that may reinforce alcohol consumption.
- Increase incidence of GI & upper airway cancers
- Liver cirrhosis.

Alcohol & the neurotransmitters

Alcohol effects on Central Neurotransmitters:

Alcohol inhibits **NMDA-glutamate** (excitatory) Receptors & activates **GABA**A Receptors in brain this will lead to:

- Sedative effect & CNS depression
- Impairment in memory, consciousness, alertness & learning," **Blackouts"**

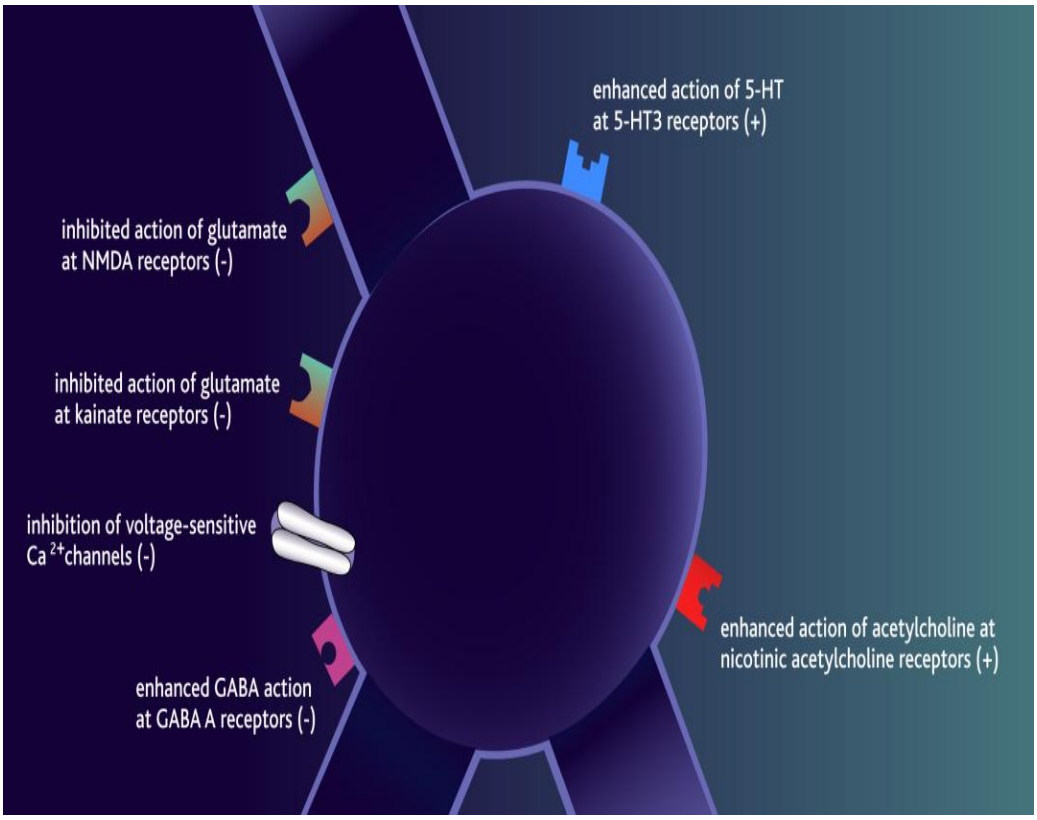
Note: A blackout is a phenomenon caused by the intake of alcohol or other substance in which long term memory creation is impaired or there is a complete inability to recall the past.

Chronic use of alcohol leads to UP-REGULATION of **NMDA**-Receptors & voltage-sensitive Ca Channels;

1- Increased NMDA activity significantly increase Ca influx to nerve cells, Ca excess can lead to cell toxicity & death. (Ca related-**brain damage**).
2- This also contributes to **alcohol tolerance** & **withdrawal** symptoms (tremors, exaggerated response & seizures).

Acute Effect of Alcohol on Brain:

- ✖ Alcohol **enhances** the excitatory action of **5-HT** & acetylcholine at **5-HT$_3$ & nicotinic acetylcholine** receptors (NAch).
- ✖ Acute alcohol exposure **inhibit** the action of NMDA at glutamate Receptors, **inhibit** voltage-sensitive Ca^{2+} channels & **enhance** the action of **GABA** at inhibitory **GABA$_A$** receptors
- ✖ Feelings of **euphoria & the 'high'** often associated with acute alcohol consumption.



Alcohol Effects on Central Neurotransmitters

GABAA & Ligand-gated Ion Channels receptors:

1-Alcohol potentiates the effects of GABA on **GABAA** receptors **causing sedation & CNS depression.**

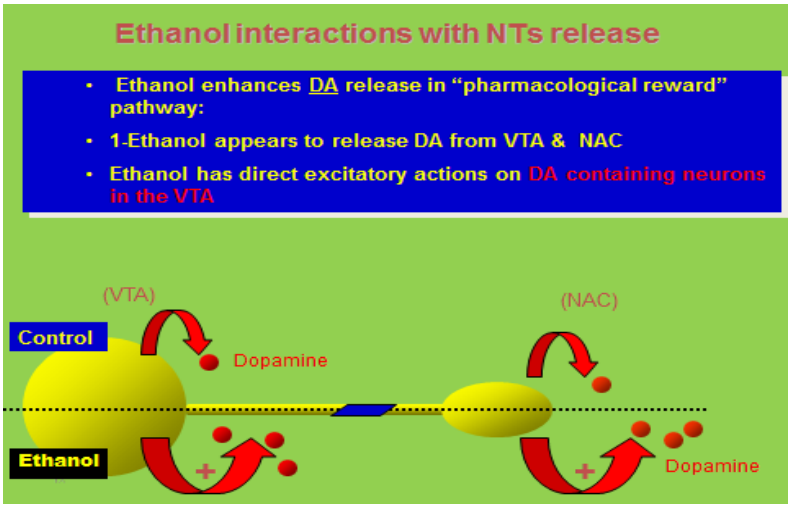
2-The activity of other ligand-gated ion channels is enhanced by Alcohol:

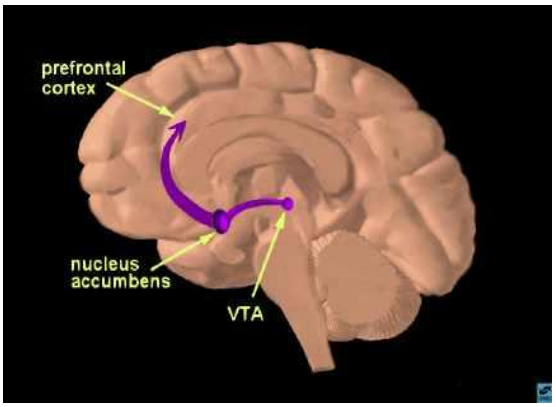
- ✓ Serotonin **5-HT$_3$** receptor (vomiting)
- ✓ The glycine receptor
- ✓ Nicotinic receptors (Nicotinic Ach Receptors)

Alcohol effect on Neurotransmitter Release:

1-Alcohol enhances **DOPAMINE** (DA) release in brain areas responsible for "**pharmacological central reinforcement/reward"**; the ventral tegmental area (VTA) & nucleus accumbens (NAC) through:

- ➢ An action that involves 5HT$_3$ Receptors
- ➢ Ethanol **directly excites DA** neurons in **VTA** & consequently, increases the release of **DA** in target areas such as **NAC**





DA: has a role in motivational behavior/ rewarding stimuli & contribute to addiction

Note: Chronic intake leads to decrease **in dopamine in NAC leading to tolerance**

Alcohol also increases release of:

- **Serotonin:** alcohol rewarding effects, tolerance & withdrawal
- **Opioid peptides**; feeling of euphoria & increase rewarding effect of alcohol.

Brain Damage

- Cerebral cortical atrophy can be detected by CT / MRI
- Dementia & brain shrinkage
- It precedes clinical emergence of major neurological & psychological deficits
- It is probably a direct toxic effect of alcohol rather than a nutritional deficiency (NMDA).

Wernicke-Korsakoff syndrome

- Is a manifestation of **thiamine** deficiency, secondary effect of alcohol abuse (severe alcoholism).
- Result from: (inadequate **nutritional** intake; uptake of thiamine from **GIT**, liver thiamine stores are due to **hepatic** steatosis /fibrosis).
- syndrome is a combined manifestation of 2 disorder.
- **Treatment:** thiamine + dextrose-containing IV fluids.

Wernicke's encephalopathy

Is acute neurologic disorder & is characterized by:

- CNS depression (mental sluggishness, confusion, Coma)
- ocular disorder (impairment of visual acuity & retinal hemorrhage
- ataxia & polyneuropathy.

Korsakoff's Psychosis

- Main symptoms are: amnesia & executive dysfunction .

Note: Thiamine is consumed during hepatic metabolism of Ethanol, hypothalamus responds to thiamine deficiency by ordering increase in hepatic ADH activity that gives enhanced Ethanol degradation

Alcoholism Tolerance:

- person must drink progressively > alcohol to obtain a given effect on brain function
- Tolerance develops with steady alcohol intake via:
  - Faster alcohol absorption
  - ***Metabolic tolerance*, hepatic enzyme induction** (Microsomal ethanol-oxidizing system)
  - ***Functional tolerance***, change in CNS sensitivity (Neuroadaptation); involve **NMDA R, GABA R, 5HT, DA** in brain that lead to reward & reinforcement.

Alcoholism withdrawal

Symptoms:

- Autonomic hyperactivity e.g. cold sweaty skin or **pulse> 100** & craving for alcohol
- Hand tremor
- Insomnia, anxiety, agitation
- Nausea, Vomiting & thirst
- transient visual/ auditory illusions
- Grand mal seizures (after 7-48 hr alc cessation)

All the previous symptoms are possibly due to Rebound **super sensitivity of glutamate** Receptorss & hypoactivity of **GABAergic Receptors.**

Chronic wks-months intake followed by stop leads to 2 stages of severe withdrawal:

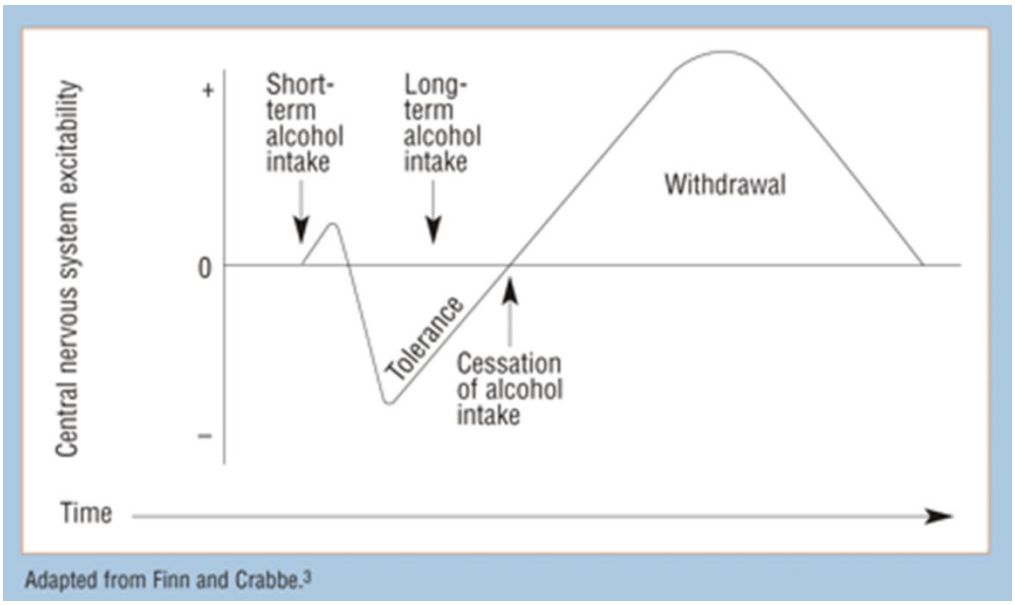
- ✖ **Aforementioned symptoms after few hours**
- ✖ **After ≥2 days *delirium tremens"* stage starts fatal; body tremors, profuse sweating, delirium & hallucinations, intense Vasodilation, fever, & severe tachycardia .**

Delirium tremens maybe due to:

- ✓ **rebound *β-adrenoceptor super-sensitivity***
- ✓ **hyperactivity of neural adaptive mechanism (neuroadaptation) no longer balance by inhibitory effect of alcohol & up regulation of NMDA Receptors .**

In conclusion, degree of withdrawal symptoms depends upon severity, rate & duration of preceding drinking period:

- ✖ **In mild cases: hyperexcitability**
- ✖ **In severe cases: seizures, toxic psychosis & delirium tremens.**
- ✖ **Begin after 8 hours, Peak at day 2, Diminish at day 5, Disappear 3 - 6 months.**



Adapted from Finn and Crabbe.[3]

Schematic representation of effects of alcohol exposure & withdrawal:

- ✖ zero line represents excitability of brain.
- ✖ Short-term alcohol intake produces a depression of inhibitory centers of ! cerebral cortex; results in initial symptoms of intoxication (**euphoria, exaggerated feelings of well-being, & loss of self-control)** followed by sedation.
- ✖ Long-term alcohol intake causes initial decrease with tolerance due to continued exposure to alcohol.
- ✖ Removal of alcohol causes a rebound stimulatory effect, increasing excitability in nervous system.

Management of alcoholism withdrawal

- ✖ Substituting a long-acting sedative hypnotic drug for alcohol & then tapering the dose. Such as *long*-BDZs (**chlordiazepoxide, diazepam)** OR *short* acting are **preferable (lorazepam)**
- ✖ Efficacy: IV/ po(oral)
- ✖ 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.**
- ✖ **Clonidine (α_2 agonist); inhibit** enhanced sympathetic Norepinephrine release.
- ✖ **Propranolol**; inhibit action of exaggerated sympathetic activity
- ✖ **Naltrexone**; po, an opioid antagonist, reduce **psychic craving** for alcohol in abstinent patients & reduce relapse.
- ✖ **Acamprosate**; a weak **NMDA-R** antagonist & **GABA activator**, reduce psychic craving. It is given po for 3- 12 months to alcohol dependent patients to inhibit neuronal excitability.

For adjunctive Treatment of alcohol dependence:

- ✖ **Disulfiram** (250 mg daily) blocks hepatic **AlDH**, this will increase blood acetaldehyde conc.
- ✖ If alcohol + disulfiram = extreme discomfort & disulfiram Ethanol reactions: Vasodilation, flushing, hotness, cyanosis, tachycardia, dyspnea, palpitations & throbbing headache.
- ✖ **Disulfiram-induced symptoms render alcoholics they become afraid from drinking alc**ohol.
- ✖ It has rapid GIT absorption, max effect within 2-4 hrs, & given after **12-24 hrs** of last alcohol drink.