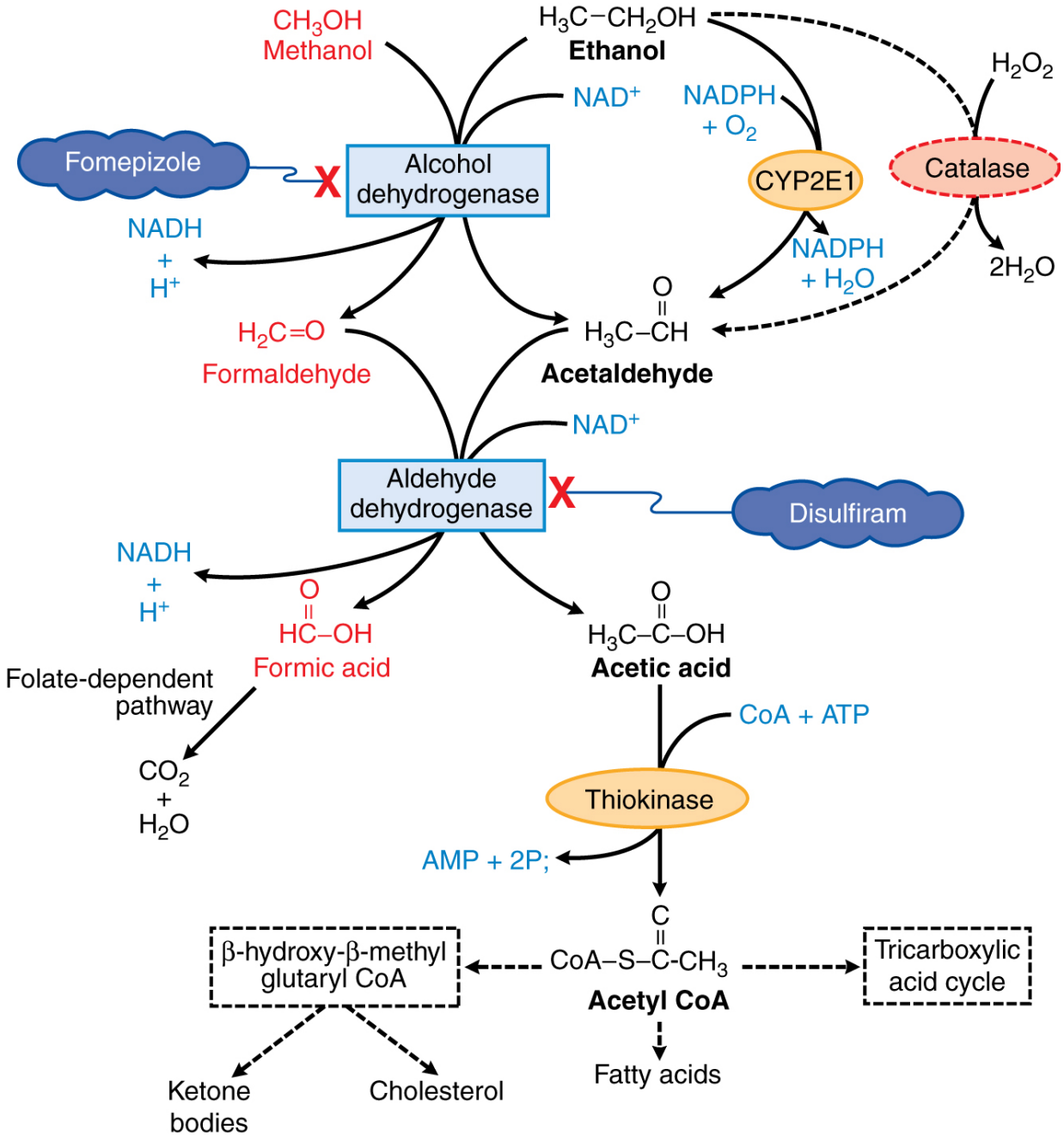
Alcohols

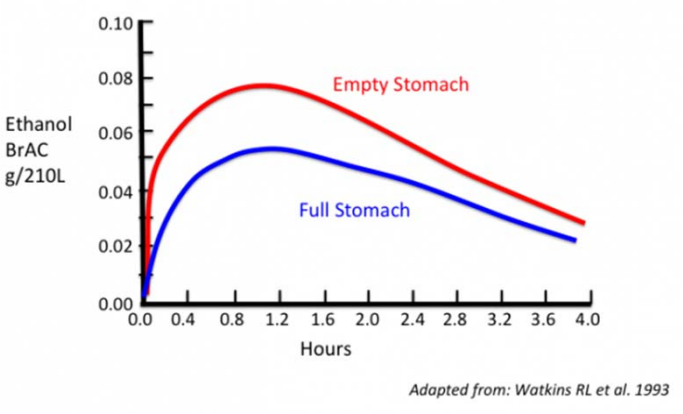
- history:
  - Old Testament (Moses)
  - Ancient Aegypt
  - Roman Empire
  - Medieval ages
  - Industrial revolution
- „most commonly abused drug”
- „French paradox”
- main types:
  - ethyl-alcohol(ethanol)
  - methyl-alcohol(methanol)
  - ethylen-glycol



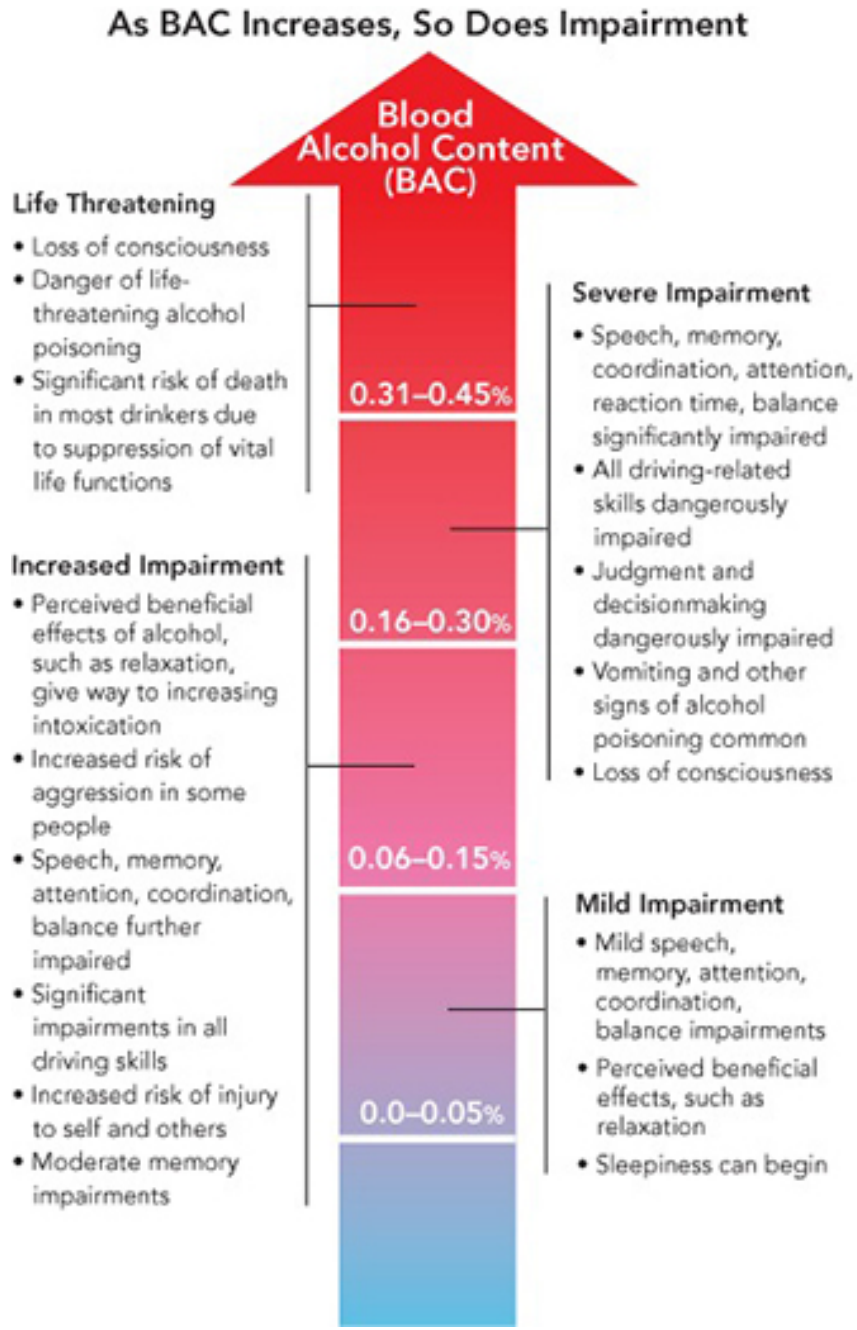
NAD depletion:

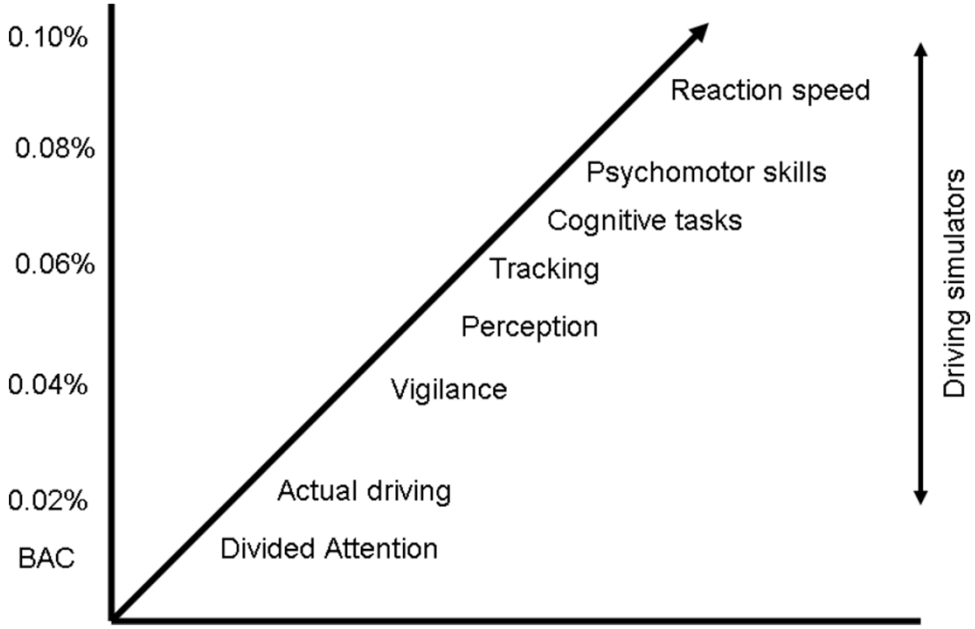
Citric acid cycle metabolites and lactate accumulation: cirrhosis and impaired glycogenolysis

Ethanol PK



- water-soluble
- rapid absorption (stomach, small intestine)
- rapid distribution, CNS („well perfused”) Vd=38L/70Kg!
- metabolized in the liver
- ADH (ethanol→acetaldehyde), ADH1A, ADH1B, AD1C
- MEOS (CYP2E1) (when ADH is saturated)
- ALDH (acetaldehyde →acetic acid), (mutation:ALDH2*2)
- excreted by kidney, lungs
- Exhaled air contains 0.05% of the plasma cc. (breathalyzer test)
- BAC (blood alcohol concentration) e.g.: 0.08% is 80 mg/dL


As BAC Increases, So Does Impairment
Blood Alcohol Content (BAC)
Life Threatening
• Loss of consciousness
• Danger of life-threatening alcohol poisoning
• Significant risk of death in most drinkers due to suppression of vital life functions
Increased Impairment
• Perceived beneficial effects of alcohol, such as relaxation, give way to increasing intoxication
• Increased risk of aggression in some people
• Speech, memory, attention, coordination, balance further impaired
• Significant impairments in all driving skills
• Increased risk of injury to self and others
• Moderate memory impairments
0.31–0.45%
0.16–0.30%
0.06–0.15%
0.0–0.05%
Severe Impairment
• Speech, memory, coordination, attention, reaction time, balance significantly impaired
• All driving-related skills dangerously impaired
• Judgment and decisionmaking dangerously impaired
• Vomiting and other signs of alcohol poisoning common
• Loss of consciousness
Mild Impairment
• Mild speech, memory, attention, coordination, balance impairments
• Perceived beneficial effects, such as relaxation
• Sleepiness can begin


0.10%
0.08%
0.06%
0.04%
0.02%
BAC
Reaction speed
Psychomotor skills
Cognitive tasks
Tracking
Perception
Vigilance
Actual driving
Divided Attention
Driving simulators

Alcohol intoxication (acute)

- BAC (mg/dl) symptoms
- 50-100 sedation, „subjective high”, slower reactions
- 100-200 impaired motorium, slurred speech, ataxia
- 200-300 emesis, stupor
- 300-400 coma, blackout
- >500 respiratory depression, death

- Intake of alcohol begins during adolescence. Ninety percent of high school seniors have tried alcohol during their life times and 30% report daily use. Chronic abuse occurs much later.

- A. Pharmacology
- Alcohol is readily dissolved in water and lipids and thus, distributes very evenly throughout the body. It crosses the blood-brain-barrier as well as the placenta without difficulty.

MOA

- 1. Affects several ion channels:
- a. NMDA receptor => allosteric inhibitor. Physical dependence/withdrawal. Reinforcement. Behavioral desinhibition.
- b. GABAA receptor => allosteric facilitator. Tolerance.
- c. 5-HT3 receptor => sedative, antianxiety effects.
- d. L-type calcium channel => allosteric modulator.

MOA2

- 2. CNS Control
- a. Alcohol effects in the cerebellum => disturb equilibrium and posture.
- b. Alcohol effects in hippocampus => disturb memory formation and retrieval.
- c. Alcohol in brainstem and medulla => disturb respiratory centers.

Alcohol intoxication (acute)

- CNS:
  - inhibiting glutamate R (NMDA channel)
  - enhancing the action of GABA on GABAAR
  - blocking VG sodium/calcium channels
  - activating VG potassium channels
  - release of β endorfins
- Heart
  - cardiodepressive effect
- Respiratory system
  - Depression
- Smooth muscle
  - vasodilation

Acute Intoxication/Overdose

- Loss of inhibition, anxiolysis, sedation, decreased motor coordination. Slowed and slurred speech, ataxia, nystagmus, drowsiness coma, confusion; reflexes are low, respiratory depression or apnea, low blood pressure death.

Alcohol chronic intoxication

- Liver and GIT
  - fatty liver, alcohol induced hepatitis, cirrhosis
  - enzyme induction (early phases)
  - chronic pancreatitis
  - malabsorption syndrome
- CNS
  - neurotoxicity (Wernicke-Korsakoff syndrome)
  - tolerance –dependence –alcohol withdrawal syndrome
  - delirium tremens
- Cardiovascular system
  - Cardiomyopathy
  - heart failure
  - Arrhythmia
  - CHD
- Blood/Immune system
  - Anaemia
  - Infections
- Fetal alcohole syndrome
  - intrauterine growth retardation
  - microcephaly
  - abnormalities in development of midfacial region

Fetal Alcohol Syndrome (FAS)

FIGURE 4 Microcephaly and normal head circumference in children with FAS. [Printed with permission from: Streissguth A. P., and Little, R. E. (1994). Unit 5: Alcohol Syndrome: Second Edition, of the Project Cork Institute Medical School Curriculum (slide lecture series) on *Biomedical Education: Alcohol Use and Its Medical Consequences,* produced by Dartmouth Medical School.]

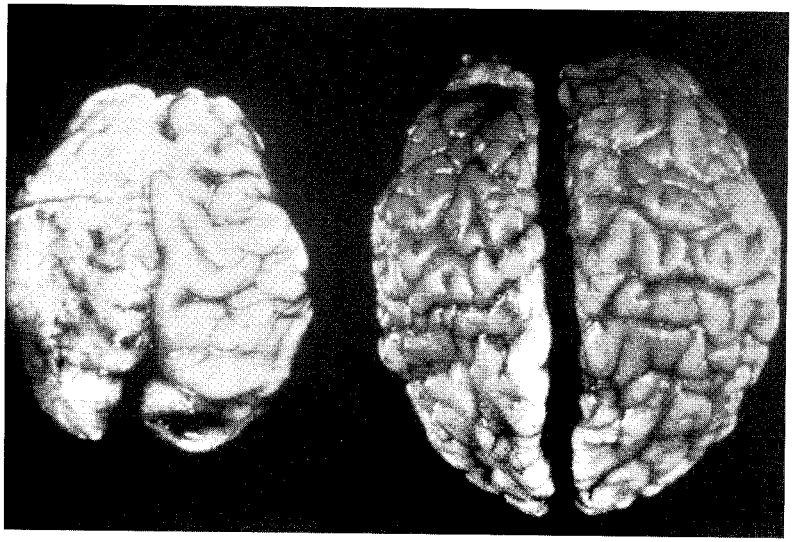


FIGURE 5 Two human brains. Normal brain (right) of an infant who died from causes other than FAS. (Left) Brain of an infant with FAS. [Reprinted with permission from the Project Cork Institute.]

Children exposed to alcohol in utero may exhibit a wide range of developmental disabilities and cognitive and behavioral deficits that reflect damage to the developing neurons. These effects may include: mental retardation, attention deficit disorders, perceptual problems, memory and learning disabilities, and psychomotor dysfunction. Fetal Alcohol Syndrome (FAS), which is characterized by central nervous system impairments, growth retardation and characteristic facial dysmorphology is the most severe, manifestation of alcohol neuratogenesis.

Management of acute ethanol intoxication

- prevent respiratory depression
- prevent aspiration (vomitus)
- glucose i.v.
- thiamine i.v. (Vitamin B1)
- prevent electrolyte disturbances: antiemetic drugs (metoclopramide, Vitamin B6)

Alcohol withdrawal syndrome

- When an alcoholic stops drinking, withdrawal symptoms begin within six to 48 hours and peak about 24 to 35 hours after the last drink. During this period the inhibition of brain activity caused by alcohol is abruptly reversed. Stress hormones are over-produced and the central nervous system becomes over-excited. Depending on severity, withdrawal symptoms may include the following:
- Fever.
- Rapid heart beat.
- Changes in blood pressure either higher or lower.
- Extremely aggressive behavior.
- Hallucinations and other mental disturbances.
- Seizures occur in about 10% of adults during withdrawal, and in about 60% of these patients, the seizures are multiple. The time between the first and last seizure is usually six hours or less.
- About 5% of alcoholic patients experience delirium tremens, which usually develops two to four days after the last drink.

Delirium tremens

- Insomnia, tremulousness, REM rebound, reflexes are high, weakness, anorexia, orthostatic hypotension, sweating, agitation
- Delirium, vivid auditory and visual hallucinations; convulsions and seizures (probably caused by increase NMDA receptor number and hyperexcitability), may generate “status epilepticus”.
- Disorientation, paranoid delusions, hyperthermia dehydration, cardiovascular collapse.
- Risk of death

Treatment of withdrawal syndrome

- Benzodiazepines.
- To inhibit nerve-cell excitability in the brain.
- Relieve withdrawal symptoms.
- Help prevent progression to delirium tremens.
- Reduce the risk for seizures.
- Benzodiazepines may be administered intravenously or orally, depending on the severity of symptoms. These drugs vary in how long they are effective.
- diazepam (Valium Seduxen)
- lorazepam (Ativan)
- oxazepam (Serax)
- alprazolam (Xanax)
- midazolam (Dormicum Versed)
- benzodiazepines are usually not prescribed for more than two weeks or administered for more than three nights per week

Treatment of alcoholism

- disulfiram (Antaethyl®)
- blocking ALDH → acetaldehyde↑, „hangover”
- sweating, facial flushing, nausea, vomiting, hypotension, confusion
- Acamprosate
- NMDA antagonist, GABAAR activator
- effects based on receptor occupancy –partial agonism
- naltrexone

Treatment of Dependence

- Detox Center/Clinic
- Disulfiram (antabuse) *
- CCC (citrate calcium carbamate)*

- *Both of these drugs are acetaldehyde dehydrogenase blockers.
- Drinking alcohol with these drugs produces increased concentration of acetaldehyde and this makes the person sick.
- Sometimes tranquilizers and antidepressants are given to relieve the anxiety.
- DETOX is best in a hospital setting.
- AAA to prevent relapse.

Methanol

- industrial application, detergents
- accidental/suicide intoxication
- absorbed from skin, GIT
- metabolized by ADH, ALDH
- (methanol→formaldehyde→formic acid)
- Symptoms
  - visual disturbances (snow storm)→(retina destruction)
  - nausea, vomitus, seizures (metabolic acidosos)
  - respiratory distress, coma

Treatment of methanol intoxication

- decontamination
- ethanol (p.o., i.v.) –saturating ADH
- fomepizole –inhibitor of ADH
- alkalization (Na_2HCO_3)
- Haemodialysis
- support of respiration
- anti seizure therapy

Ethylene glycol intoxication

- windshield washing, anti-freeze formulations
- accidental/suicide intoxication
- rapid absorption from GIT
- metabolized by ADH
- Symptoms
  - Headache
  - nausea, vomitus, seizures (metabolic acidosos)
  - acute renal failure
  - respiratory distress, coma

Treatment of ethylene glycol intoxication

- decontamination
- ethanol (p.o., i.v.) –saturating ADH
- fomepizole –inhibitor of ADH
- alkalization (Na_2HCO_3)
- haemodialysis
- support of respiration
- anti-seizure therapy