Alcohols

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Pharmacology II

Alcohols

- **Ethanol** is the most important alcohol of pharmacologic interest.
- It has anxiolytic and sedative effects, but its toxic potential outweighs its benefits.
- Its abuse causes major medical and socioeconomic problems.
- Other alcohols of toxicologic importance are **methanol** and **ethylene glycol**.

Ethanol

- Two enzyme systems metabolize ethanol to acetaldehyde.

1. **Alcohol dehydrogenase (ADH)**

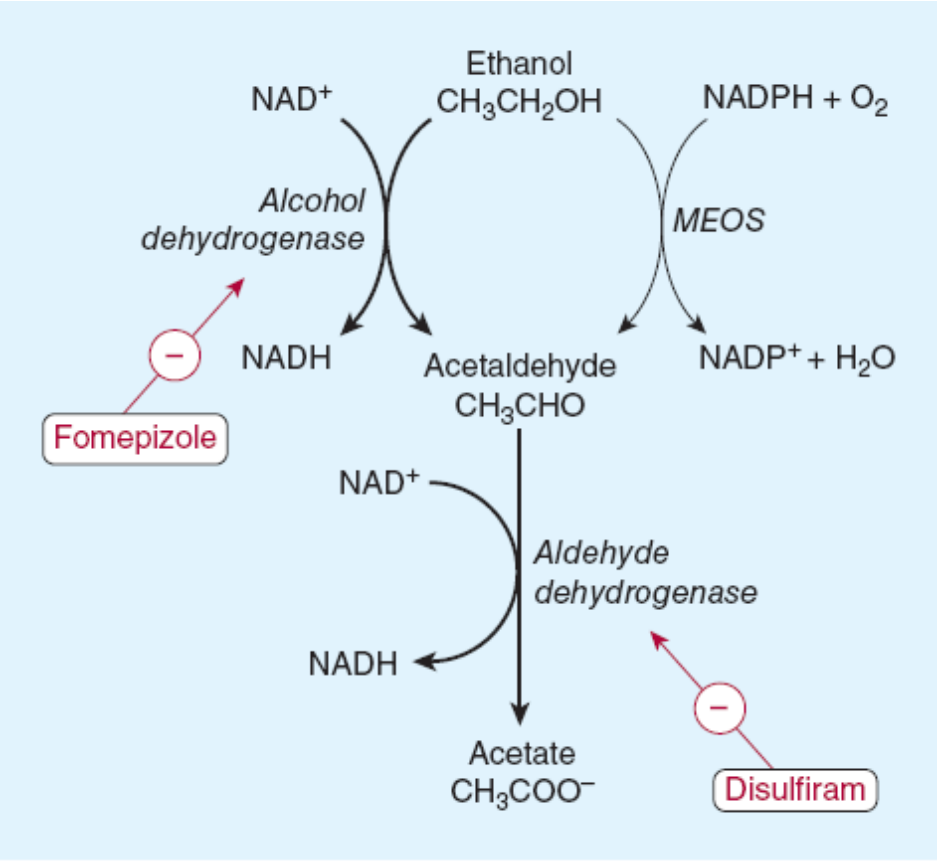
- NAD+-dependent enzymes, found mainly in the liver.
- It accounts for the metabolism of low to moderate doses of ethanol.
- Has zero-order kinetics, resulting in a fixed capacity for ethanol metabolism.

2. **Microsomal ethanol-oxidizing system (MEOS)**

- Contributes significantly to ethanol metabolism at blood ethanol levels higher than 100 mg/dL.

Ethanol

- **Acetaldehyde Metabolism**
- Acetaldehyde formed from the oxidation of ethanol by either ADH or MEOS is rapidly metabolized to acetate by aldehyde dehydrogenase, a mitochondrial enzyme found in the liver and many other tissues.
- Aldehyde dehydrogenase is inhibited by **disulfiram.**



Alcohol-Drug Interactions

- Interactions between ethanol and other drugs can have important clinical effects resulting from alterations in the pharmacokinetics or pharmacodynamics of the second drug.
  - Prolonged intake of alcohol without damage to the liver can enhance the metabolic biotransformation of other drugs.
    - Ethanol-mediated induction of hepatic cytochrome P450 enzymes is particularly important with regard to acetaminophen. Chronic consumption of three or more drinks per day increases the risk of hepatotoxicity due to toxic or even high therapeutic levels of acetaminophen as a result of increased P450-mediated conversion of acetaminophen to reactive hepatotoxic metabolites.
    - Current FDA regulations require that over-the-counter products containing acetaminophen carry a warning about the relation between ethanol consumption and acetaminophen-induced hepatotoxicity.

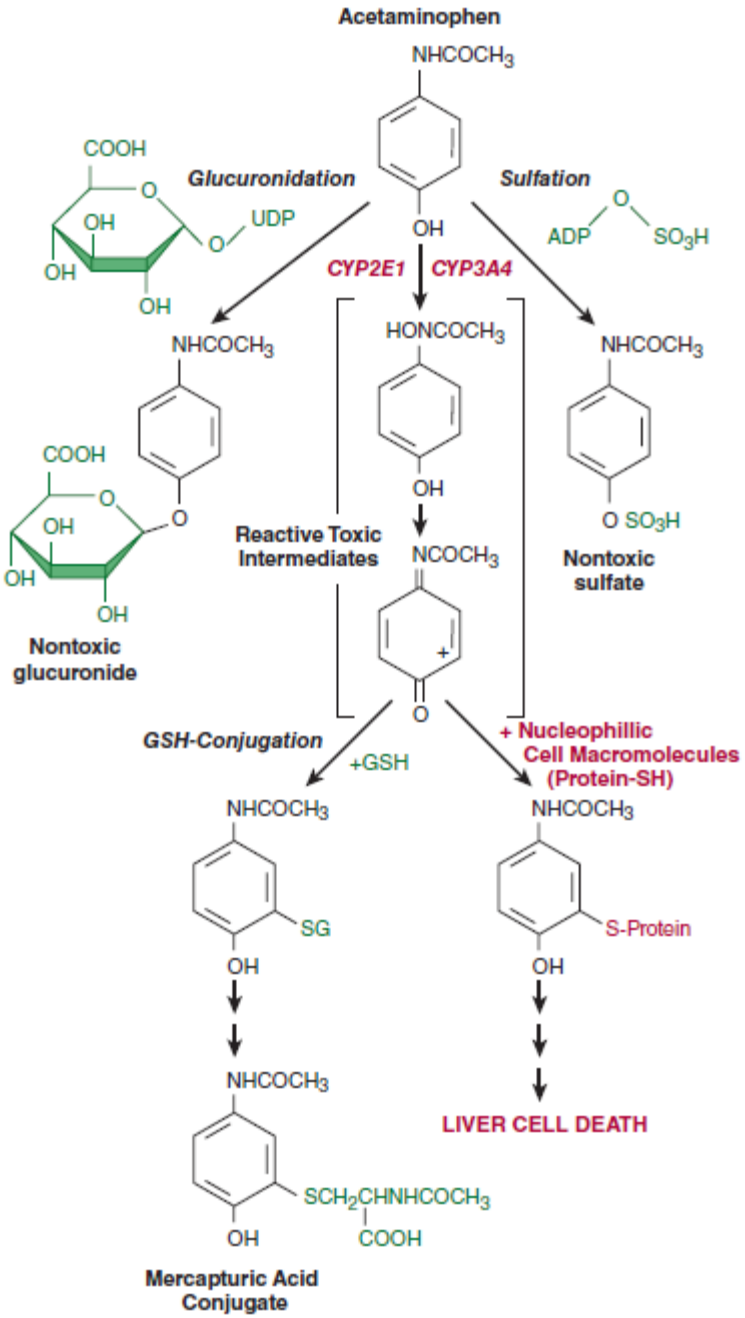


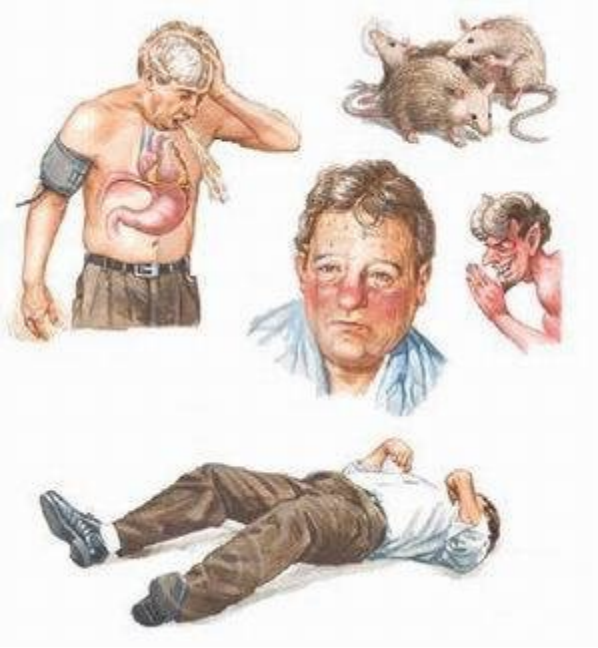
FIGURE 4–5 Metabolism of acetaminophen (top center) to hepatotoxic metabolites. GSH, glutathione; SG, glutathione moiety.

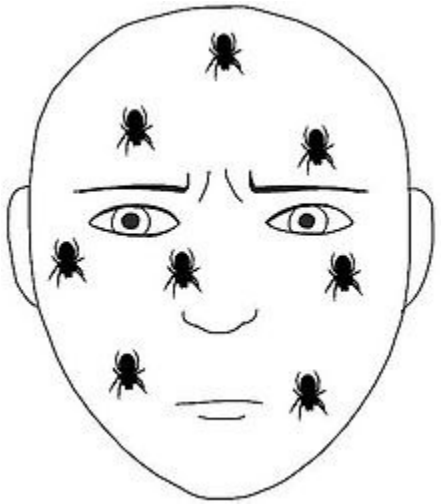
Alcohol-Drug Interactions

- In contrast, acute alcohol use can inhibit metabolism of other drugs because of decreased enzyme activity or decreased liver blood flow.
  - Phenothiazines, tricyclic antidepressants, and sedative-hypnotic drugs are the most important drugs that interact with alcohol by this **pharmacokinetic** mechanism.
- **Pharmacodynamic** interactions are also of great clinical significance.
- The additive CNS depression that occurs when alcohol is combined with other CNS depressants, particularly sedative-hypnotics, is most important.

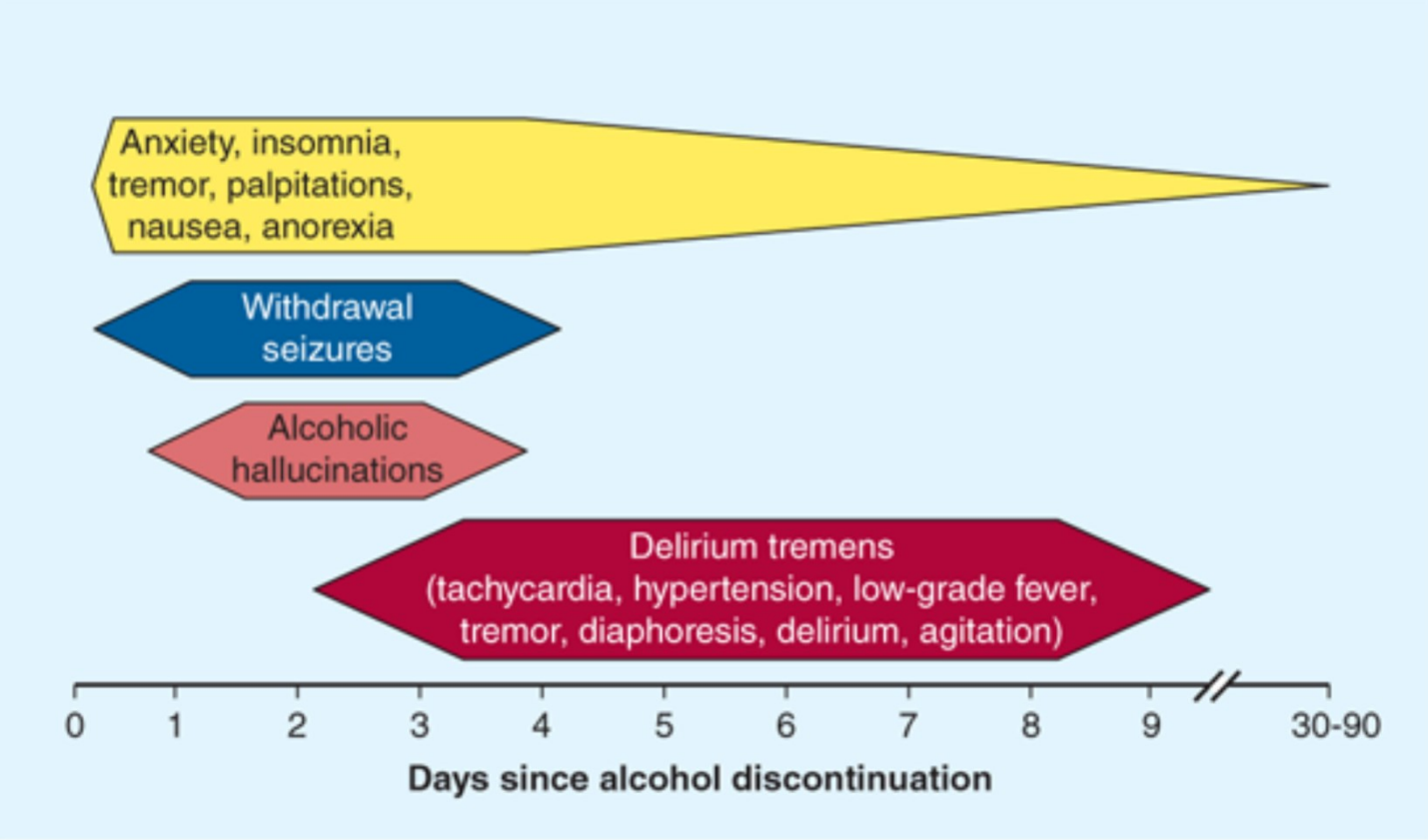
Alcohol Withdrawal Symptoms

- In individuals physically dependent on ethanol, discontinuance can lead to a withdrawal syndrome characterized by **insomnia, tremor, anxiety**, and, in severe cases, life-threatening **seizures** and **delirium tremens** (which is characterized by delirium, agitation, autonomic nervous system instability, low-grade fever).
- Peripheral effects include nausea, vomiting, diarrhea, and arrhythmias.





Alcohol Withdrawal Symptoms



Source: Bertram G. Katzung, Anthony J. Trevor: Basic & Clinical Pharmacology, 13th Ed.
www.accesspharmacy.com

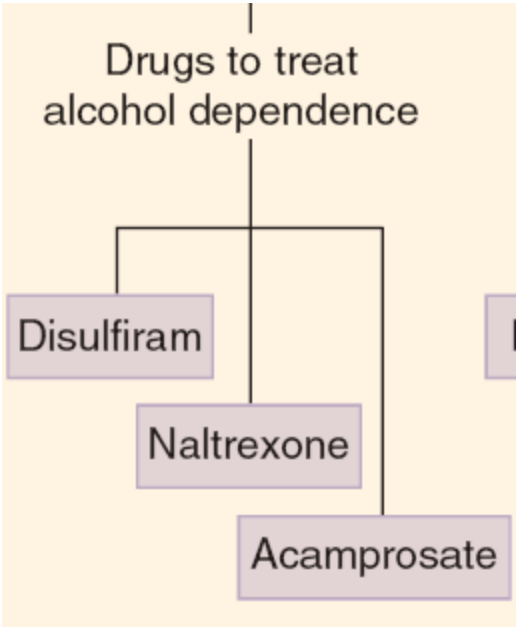
Management of Alcohol Withdrawal Symptoms

- The withdrawal syndrome is managed by:

1. correction of electrolyte imbalance
2. administration of thiamine
3. a sedative-hypnotic.
   - A long-acting benzodiazepine (eg, diazepam, chlordiazepoxide) is preferred unless the patient has compromised liver function, in which case a short-acting benzodiazepine with less complex metabolism (eg, lorazepam) is preferred.

Treatment of alcoholism (alcohol dependence)

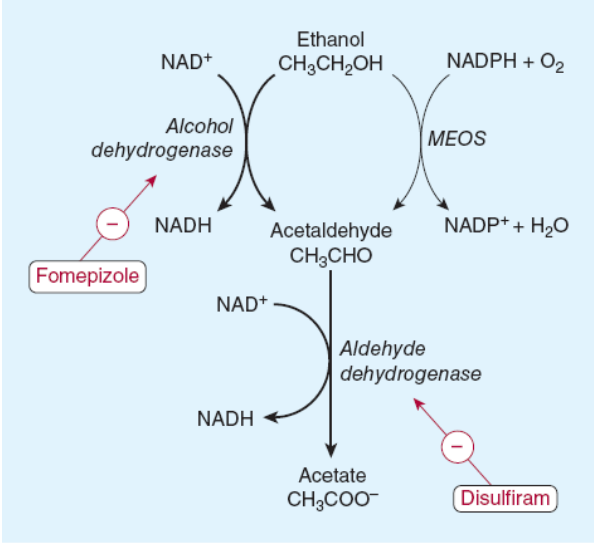
- Alcoholism is a complex socio-medical problem, characterized by a high relapse rate.
- Three drugs—**disulfiram**, **naltrexone**, and **acamprosate**—have FDA approval for adjunctive treatment of alcohol dependence.



Treatment of alcoholism (alcohol dependence)

1. Disulfiram:

- Disulfiram blocks the oxidation of acetaldehyde to acetic acid by inhibiting aldehyde dehydrogenase. This results in the accumulation of acetaldehyde in the blood, causing **flushing, throbbing headache, nausea, vomiting, sweating, hypotension, and confusion** which occur within a few minutes after an individual taking disulfiram drinks alcohol.
- Disulfiram has found some use in the patient seriously desiring to stop alcohol ingestion. A conditioned avoidance response is induced so that the patient gives up alcohol to prevent the unpleasant effects of disulfiram-induced acetaldehyde accumulation.



Treatment of alcoholism (alcohol dependence)

2. **Naltrexone:**

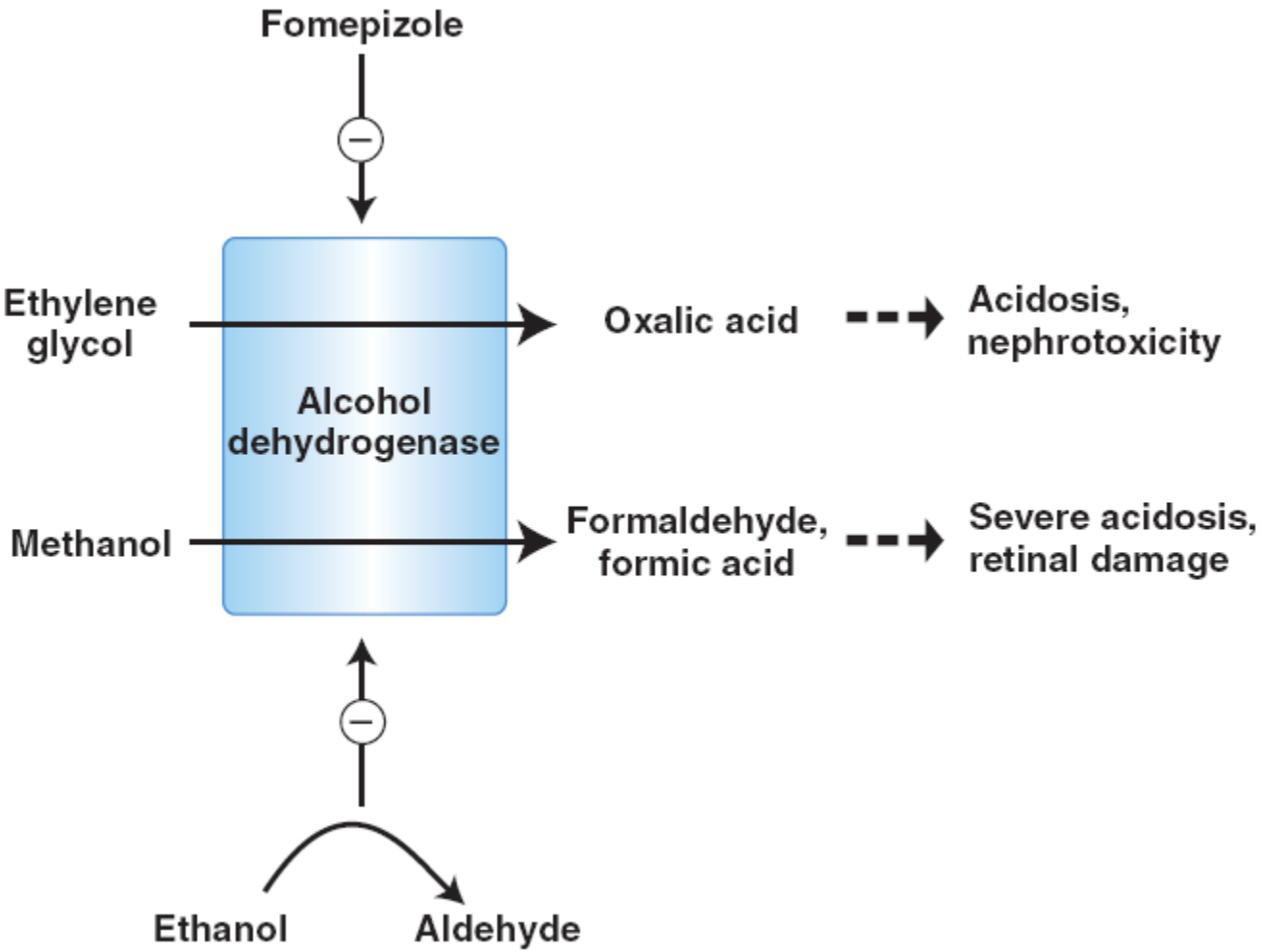
- Naltrexone is a long-acting opiate antagonist that should be used in conjunction with supportive psychotherapy.
- Studies in experimental animals first suggested a link between alcohol consumption and opioids. Injection of small amounts of opioids was followed by an increase in alcohol drinking, whereas administration of opioid antagonists inhibited self-administration of alcohol.
- Naltrexone is better tolerated than disulfiram and does not produce the aversive reaction that disulfiram does.
- The combination of naltrexone plus disulfiram should be avoided, since both drugs are potential hepatotoxins.

Treatment of alcoholism (alcohol dependence)

3. Acamprosate:

- Acamprosate is an agent used in alcohol dependence treatment programs with an as yet poorly understood mechanism of action.
  - Acamprosate has many molecular effects including actions on GABA, glutamate, serotonergic, noradrenergic, and dopaminergic receptors.
- Acamprosate reduced short-term and long-term (more than 6 months) relapse rates when combined with psychotherapy.

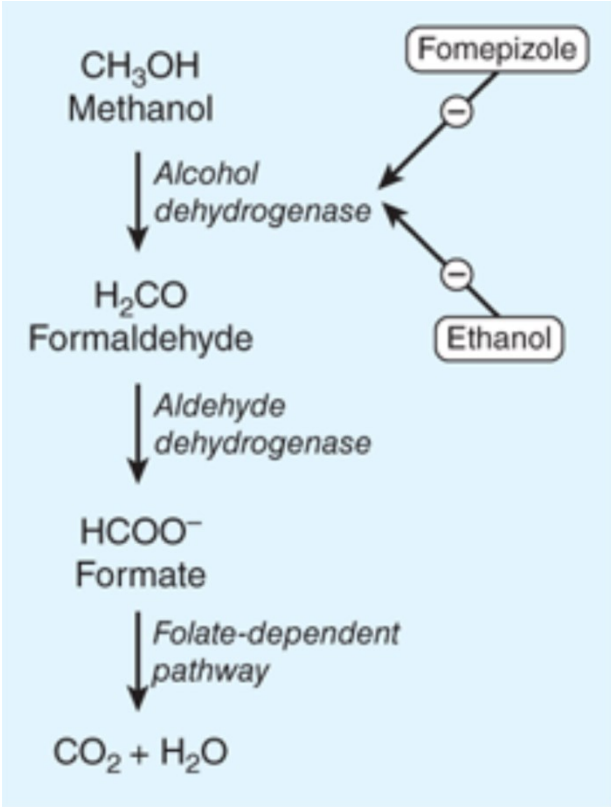
Other Alcohols



Other Alcohols

A. Methanol

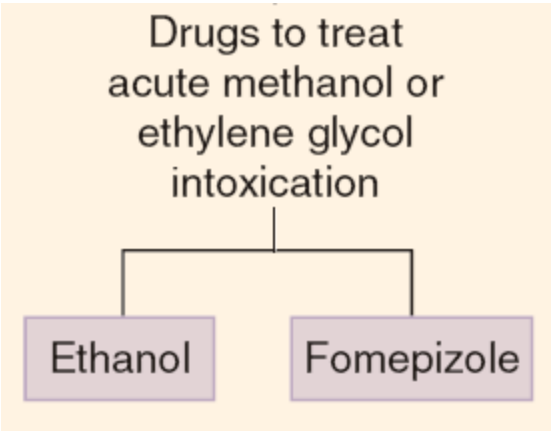
- Intoxication causes visual dysfunction, gastrointestinal distress, shortness of breath, loss of consciousness, and coma.
- Since the conversion of methanol to its toxic metabolites is relatively slow, there is often a delay of 6–30 hours before the appearance of severe toxicity.
- The formation of formaldehyde is reduced by prompt intravenous administration of **fomepizole,** an inhibitor of alcohol dehydrogenase, or **ethanol,** which competitively inhibits alcohol dehydrogenase oxidation of methanol.



Other Alcohols

B. Ethylene Glycol

- Industrial exposure to ethylene glycol (by inhalation or skin absorption) or self-administration (eg, by drinking antifreeze products) leads to severe acidosis and renal damage from the metabolism of ethylene glycol to oxalic acid.
- Prompt treatment with intravenous **fomepizole** or **ethanol** may slow or prevent formation of this toxic metabolite.
- Hemodialysis effectively removes ethylene glycol and its toxic metabolites and is recommended for patients with a serum ethylene glycol concentration above 50 mg/dL, significant metabolic acidosis, and significant renal impairment.



QUESTIONS??