Learning Objectives
1. Know effects of alcohol use (acute and chronic)
2. Understand the pharmacodynamic and pharmacokinetic factors that regulate alcohol
3. Know drug interactions and adverse effects

Overview
Ethyl Alcohol or Ethanol: sedative-hypnotic drug
- Approximately 75% of people in US drink alcohol
- "Dose": 1 serving has 14 grams of alcohol (most other drugs are taken in milli- or micro-gram doses)
- Consumption of 1 serving by 70 kg person produces ~30 mg% although this varies by many factors (rate, gender, body weight, water percentage, rates of metabolism and stomach emptying)

Levels of ethanol:
- 20-30 mg/dl: impaired judgement
- 80-100 mg/dl: legally intoxicated
- >150 mg/dl: gross intoxication
- 400 mg/dl often fatal due to respiratory depression, coma (depends on history)

Acute Effects
a. Pharmacological
   - CNS: sedation, anxiolytic, ataxia
   - GI: irritation, stimulate secretion
   - Renal: diuresis
   - Cardiovascular: cutaneous vasodilation, elevation of HDL
   - Higher doses (intoxication): increased reaction time, diminished fine motor control, impulsivity
   - More pronounced in women: size, water:weight ratio, less gastric ADH
   - Relatively low therapeutic index, no specific antagonist

1. Absorption and Distribution
   - Absorption: rapidly absorbed into bloodstream from stomach and small intestine
     - Peak levels (in fasting person) at 30-40 min; food delays absorption
     - More ethanol broken down if food is present
   - Small intestine absorbs ~85%

2. Distribution/Elimination
   - Distributed throughout fluid compartment
   - Liver 90-95% elimination
   - Lungs and kidney 5-10% elimination

3. CNS Mechanisms
   - Alcohol interacts with multiple systems (i.e. no specific ETOH receptor)
   - Disrupts inhibitory/excitatory balance in brain: enhances inhibitory, decreases excitatory
   - Targets include:
     - Ionotropic Receptors: GABA, nicotinic ACh, NMDA and kainate
     - Enzymes: intracellular messenger: kinases and signaling enzymes
**d. Metabolism**

Average adult metabolizes ~10 ml/hr (10 oz. beer, 3.5 oz. wine or 1 oz. 80 proof spirits) i.e. one standard drink every 60-90 minutes

ADH = Alcohol Dehydrogenase, rate limiting step

AcDH = Acetaldehyde Dehydrogenase

1. Alcohol $\rightarrow$ Acetaldehyde

2. Acetaldehyde $\rightarrow$ CO$_2$ + H$_2$O

**1. Alcohol Dehydrogenase (ADH): primary pathway**
- Mainly in liver, also found in stomach (note women have less in stomach)
- Saturated at low alcohol concentrations
- Metabolizes ~90% of alcohol

**b. MEOS: microsomal ethanol oxidizing system (cytochrome P450)**
- Contributes when large amounts are consumed and ADH is saturated
- Inducible by chronic consumption therefore increases clearance of alcohol and other drugs
- Produces acetaldehyde and reactive oxygen species that may cause cell damage

**2. Chronic**

- **Hepatic**: liver disease most common effect of chronic alcohol consumption
  - Fatty infiltration, hepatitis, cirrhosis, liver failure

- **Nutritional deficiencies**: decreased absorption, impaired utilization of nutrients
  - B complex deficiency (esp. thiamin) affects nervous system

- **Immune**: higher rate of infection (esp. respiratory infection), poor wound healing

- **Cancer**: increased cancer risk; oral and liver

**Teratogenic: Fetal Alcohol Syndrome**

- Stunted growth
- Craniofacial abnormalities
- CNS dysfunction

**NO SAFE DOSE**

**1. Alcohol $\rightarrow$ Acetaldehyde**

**a. Alcohol Dehydrogenase (ADH): primary pathway**
- Mainly in liver, also found in stomach (note women have less in stomach)
- Saturated at low alcohol concentrations
- Metabolizes ~90% of alcohol

**b. MEOS: microsomal ethanol oxidizing system (cytochrome P450)**
- Contributes when large amounts are consumed and ADH is saturated
- Inducible by chronic consumption therefore increases clearance of alcohol and other drugs
- Produces acetaldehyde and reactive oxygen species that may cause cell damage

**2. Acetaldehyde $\rightarrow$ CO$_2$ + H$_2$O

- Oxidized in liver by aldehyde dehydrogenase
- Polymorphisms: genetic deficiency (Asians)
- Inhibited by disulfiram

**CNS**: tolerance and physical dependence, psychological dependence, Korsakoff syndrome (memory deficit), Wernicke’s encephalopathy (mental confusion, delirium)

**Teratogenic**: Fetal Alcohol Syndrome

- Stunted growth
- Craniofacial abnormalities
- CNS dysfunction

**NO SAFE DOSE**

**a. Toxicity**
- Acute toxicity: respiratory depression
- Management of intoxication: prevent respiratory depression and a aspiration of vomit; may need to administer glucose, electrolyte solution

**f. Drug Interactions**
- Additive CNS depression: barbiturates, BZs, nitrous oxide, volatile solvents
- Additive depression between alcohol and benzodiazepines: can produce respiratory depression, hypotension, hypothermia, and coma
- Alcoholic beverages with tyramine: hypertension with MAO inhibitors
f. Drug Interactions, con’t

<table>
<thead>
<tr>
<th>Drug Class</th>
<th>Effect</th>
</tr>
</thead>
<tbody>
<tr>
<td>Analgesics (pain killers)</td>
<td>Increased depression of central nervous system</td>
</tr>
<tr>
<td>Anti-coagulants</td>
<td>Increased anti-clotting effect; easy bruising</td>
</tr>
<tr>
<td>Antihistamines</td>
<td>Increased depression of central nervous system</td>
</tr>
<tr>
<td>Insulin</td>
<td>Increased chance of hypoglycemia</td>
</tr>
</tbody>
</table>

Drug Interactions: Pharmacokinetic

P450 isn’t major factor in ethanol metabolism but is induced by chronic consumption, which may increase clearance of drugs:

- Chronic: MEOS induction stimulates metabolism
- Decreases levels of barbs, hydantoins, isoniazid, warfarin
- Increases toxicity of acetaminophen due to production of toxic metabolite

Route ethanol decreases clearance of these same drugs because of competition for the enzyme (phenytoin, warfarin, tricyclic antidepressants, sedative-hypnotic drugs)

Hepatotoxicity:
- Acetaminophen/alcohol
- Can be potentiated by drugs that induce hepatic enzymes (barbs, carbamazepine, phenytoin)

Aspirin increases ethanol bioavailability by inhibiting gastric ADH

g. Tolerance: reduced behavioral or physiological response to same dose of ethanol

- Limited tolerance to lethality so only small increase in lethal dose
- Cross tolerance with benzodiazepines

Treatment

- Disulfiram (Antabuse)
  - Inhibits aldehyde dehydrogenase
  - Acetaldehyde concentration increases 5X-10X
  - Patients must avoid all alcohol (ingested and topical)
  - Produces vasodilatation: flushing, throbbing headache
  - Respiratory difficulties, nausea, vomiting, sweating, thirst, chest pain, hypotension, uneasiness, weakness, vertigo, blurred vision, confusion
  - Effects start 5-10 min after ingestion and last 30 min to several hours
  - Note: disulfiram inhibits hepatic microsomal drug-metabolizing enzymes and interferes with metabolism of phenytoin, chloral hydrate, barbiturates, others

- Psychologically: craving and drug seeking

- Naltrexone (ReVia): approved 1994
  - Related to naloxone but has higher bioavailability and longer duration of action
  - Helps maintain abstinence by reducing urge to drink, not effective in all patients

- Acamprosate: used in Europe
  - Mechanism unknown; may affect NMDA receptors
  - Decreases drinking frequency and reduces relapse
  - Generally well tolerated; main side effect is diarrhea

- Ondansetron: 5HT₃ antagonist (anti-emetic drug)
  - Reduces consumption in lab, currently being tested in humans

j. Clinical Uses

- Dehydrated alcohol injection near nerves or sympathetic ganglia to relieve pain from trigeminal neuralgia, inoperable carcinoma, etc.

- Treatment of methanol poisoning: methanol found in industry, also constituent of many commercial solvents (i.e. windshield washer fluid and “canned heat”)
- Ethanol is administered i.v. because it has a higher affinity than methanol for ADH, thus saturating the enzyme and preventing metabolism of methanol to formate and formaldehyde (toxic metabolites)