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Clinical Features

Alcohol Subrogates (methanol, ethylene glycol, isopropanol) see p. 703 >>, p. 703 (1) >>

Alcohol is used by 2/3 of adult population in USA

Definitions

Ethanol 1 mL = 7 kcal.

Drink = one 12-oz beer, one 4- to 5-oz glass of wine, or one mixed drink containing 1.5 oz of 80 proof spirits.

Binge drinking = ≥ 5 alcoholic drinks for men ≥ 4 for women on one occasion.

Hazardous drinking:

Men < 65 years: > 4 drinks on any one occasion or > 13 drinks per week.

Men > 65 years: women > 3 drinks on any one occasion or > 7 drinks per week.

Children, teens, with personal or family history of alcohol dependence, pregnant or breastfeeding women: any use of alcohol.

Any use before or during situations requiring attention or skill (e.g. driving).

Alcohol abuse - maladaptive episodic drinking resulting in failure to fulfill obligations, exposure to physically hazardous situations, legal problems, or social and interpersonal problems without evidence of dependence.

Alcohol dependence - frequent consumption of large amounts of alcohol over time, resulting in tolerance, psychologic and physical dependence and dangerous withdrawal syndrome.

Alcoholism - equivalent term for alcohol dependence, especially when results in significant clinical toxicity and tissue damage.

“Anglo-Saxon” or “Scandinavian” drinking pattern - greater drinking on holidays and weekends.

“Mediterranean” drinking pattern - regular alcohol consume during week, particularly with meals.

Physiology & Biochemistry

- alcohol is absorbed from stomach-duodenum-jejunum (via) can be detected in blood within 5 minutes of ingestion.
- alcohol accumulates in blood because absorption is more rapid than elimination.
- alcohol acts as CNS depressant (first reticular formation (with cerebral disinhibition), and later cerebral cortex.
- exact mechanism of action remains unclear:
  a) non-specific peripheral depression of neuronal membrane lipids.
  b) action at interface between neuronal and membrane protein.
  c) direct action on neurotransmitter-gated ion channels (incl. acetylcholine, GABA\textsubscript{A}, NMDA).

Catalolism

- mainly in liver - oxidized to acetaldehyde (via ALDEHYDE DEHYDROGENASE) to acetate (via ALDEHYDE DEHYDROGENASE) + CO\textsubscript{2} and water. see p. 702.>>
alcohol dehydrogenase polymorphism — see p. 3770

- 5:10% are excreted unchanged in urine, sweat, and expired air.
- catabolism follows zero-order kinetics\(^*\) at 70-150 mg/kg/hour (BECC falls 10-25 mg/dl/hour).
- most adults require 6 hours to metabolize 50 g dose; ingestion of only 8 g of additional ethanol/hour would maintain BEC at 100 mg/dl.
- BEC of 400 mg/dl takes 20 hours to return to zero.
- metabolism rate can be enhanced by INSECT, AMINO ACIDS, FRUCTOSE; starvation has opposite affect.

**NAME: \( T \)**
- represents adaptive change in CNS (i.e. pharmacodynamic tolerance - mechanistic similarities to learning or memory function).
- tolerance may also involve adaptive changes in neuronal membrane lipids, neurotransmitter receptors, ion channels, or intracellular secondary messenger systems that serve to counteract short-term effects of alcohol.
- provides CROSSTOLERANCE to many other CNS depressants (barbiturates, nonbarbiturate sedatives, benzodiazepines).

**ALCOHOL INTOXICATION (DRUNKENNESS)**

- depend on blood ethanol concentration (BEC), rate of climb, person's tolerance (related less to increased metabolism than to poorly understood adaptive changes in brain).
- N.B. Blood ethanol concentration alone is not reliable indicator of drunkenness!

**Mild intoxication**, - disorganization of cognitive and motor processes (first functions to be disrupted are those that depend on training and previous experience).

- All aspects of physical and mental performance are impaired by alcohol!
1. anxious/sudor and sedation (due to effects on GABA, euphoria (due to increased opiate levels), mood swings, emotional outbursts, disinhibited verbosity and behavior (restlessness, hyperactivity).
2. overconfidence (due to disinhibition - individual transiently functions better after ingestion of small amounts of alcohol).
3. increased pain threshold (other sensory modalities are unaffected).
4. nausea, vomiting.
5. enhancement of spinal reflexes (release from higher inhibiting circuits).

- during sleep, REM suppression → after few hours → REM "rebound".

**Deepening intoxication**
1. shared speech
2. loss of coordination, unsteady gait
3. systagmus, diplopia
4. impaired attention or memory

**Severe intoxication** (progressive general anesthesia of CNS functions):
1. stupor → coma (there are no distinctive clinical characteristics of alcoholic coma; may become alert and combative as BAC decreases).

**ALCOHOL BLACKOUT** - amnesia for period of intoxication, even though consciousness at time did not seem to be disturbed.
- mechanism uncertain.
- considered sign of physiologic dependence (but blackouts also occur in occasional drinkers).

**DIAGNOSIS**

- Main challenge is not to diagnose drunkenness, but not to overlook concomitant intoxication with other drugs or other causes for ataxic gait or coma!

**Odor on patient's breath** (characteristically associated with alcohol intoxication) is caused by impurities in preparation and is unreliable in diagnosing intoxication.

**Blood ethanol concentration (BEC)** (most important test to support diagnosis).
- determined by microdiffusion test; gas chromatography allows differentiation between ethanol and methanol.
- CNS concentration of alcohol parallels concentration in blood.
- through repeated consumption, humans become habituated rapidly: blood level 100 mg/dl causes drunkenness in occasional habitual drinkers, but chronic abusers can tolerate 500 mg/dl without any apparent effects.
- at any BEC, intoxication is more severe when level is rising (than when it is falling).

**Correlation of Symptoms with BEC**

\[
\begin{array}{ll}
50 \text{ mg/dl} & \text{Sedation, tranquility} \\
80 \text{ mg/dl} & \text{Legal driving limit in most USA states} \\
150 \text{ mg/dl} & \text{Euphoria / dysphoria, shyness / expansiveness, friendliness / argumentativeness. Impaired concentration, judgment, sexual inhibitions} \\
250 \text{ mg/dl} & \text{Slurred speech, ataxic gait, diplopia, nausia, tachycardia, drowsiness, labile mood (sudden bursts of anger, antisocial acts), delirium} \\
300 \text{ mg/dl} & \text{Stupor alternates with combativiness or incoherent speech, heavy breathing, vomiting} \\
400 \text{ mg/dl} & \text{Coma (death has occurred)}
\end{array}
\]
Respiratory paralysis - lethal in 50% patients

- survival is documented even at 700 mg/dl.
- to obtain BEC of 100 mg/dl, 70-kg person must drink 50 g of 100% ethanol.

Serum osmolality: (i.e. higher than predicted by sum of serum sodium, glucose, and urea).
- ethanol raises osmolality 22 mOsm/kg, for every 100 mg/dl of ethanol.
- there are no transmembrane shifts of water - hyperosmolarity does not cause symptoms.

EEG
BEC 150-250 mg/dl - increased EEG beta activity ("beta buzz");
higher concentrations - EEG slowing.

DIFFERENTIAL DIAGNOSIS
1. Head injury (esp. subdural hematoma)
2. Metabolic encephalopathies (e.g. hypoglycemia).
3. Menigitis

TREATMENT
- depends on level of consciousness:

  Conscious patient

  1. oral fluids
  2. resuscitation if hypovolemic
  3. if patient is not agitated: do not disturb
  4. if agitation:
     - isolation, calming environment, reassurance.
     - sedation with benzodiazepines

  Stuporous or unconscious patient

  1. airway, breathing, circulation
  2. nasogastric tube (if needed)
  3. intubation if patient apneic or deeply comatose
  4. parenteral ethanol

  N.B. alcohol is absorbed rapidly - gastric lavage with activated charcoal is not effective in preventing deeper intoxication! (avoid emetics or gastric lavage)

  mechanical ventilatory support (if necessary), prevent aspiration.

  keep warm with legs elevated.

  monitor BP, correct hypovolemia & acid base imbalance (ketoadicosis is possible)

  hypoglycemia is possible; if serum glucose in doubt → IV 50% GLUCOSE with parenteral THIAMINE.

  for ICP - MANNITOL, corticosteroids.

  in extreme situations (apnic or deeply comatose, esp. children, intoxication with other dialyzable drugs) remove alcohol by hemodialysis.

PROGNOSIS

- virtually all episodes resolve without sequelae.

ETHANOL-DRUG INTERACTIONS

- alcoholics often abuse barbiturates; they are cross-tolerant, but taken acutely in combination lower lethal dose of either alone.
- ethanol with CHLORAL HYDRATE ("Mickey Finn") may be especially dangerous.

- impaired judgment and respiratory depression are also hazards when ethanol is combined with hypnotics, antipsychotics, benzodiazepines, sedating antihistaminics.

- cross-tolerance of ethanol with general anesthetics → thresold to sleep induction, but synergistic interaction then increases depth and length of anesthetic stage reached.

- repeatedly used ethanol and barbiturates can increase each other's potency.

- mild disulfiram reaction occurs in combination ethanol with sulfonfylureas (e.g. TOLBUTAMIDE) or with some anticholinergics (e.g. GLUCOSE, FRUCTOSE, AMINOSULFONIC ACIDS).

- with parenteral ethanol has low therapeutic index.

ALCOHOL ABSTINENCE (WITHDRAWAL) SYNDROMES

- occurs usually when illness has interfered with alcohol intake or when alcoholic is hospitalized for illness or surgery.

- preceding alcohol intake must be:
  a) high level binge lasting matter of days
  b) regular ingestion sustained over many months.

- often by time patients reach hospital, alcohol is no longer detectable in blood!

- syndromes are self-limited - resolve with no residual effects (except mortality of delirium tremens).

PATHOPHYSIOLOGY

- related to abstinence from alcohol (not to specific dietary or vitamin insufficiency) - "rebound" phenomenon after prolonged suppression (may relate to O ABA or NMDA receptor systems) - similar to stopping other CNS depressants (e.g. barbiturates, diazepam).

- ethanol inhibits glutamate receptors (long-term ingestion → synthesis of more glutamate receptors; withdrawal → CNS excitability).

PROPHYLAXIS

- drinking alcohol only in moderation.

- for those who are abusing alcohol already, only sure way to prevent withdrawal syndromes is to continue alcohol (rarely practical in hospital setting - parenteral ethanol has low therapeutic index).

TREATMENT
Clinical Features  

1. Tremor/beta hyperactivity - occurs only in persons who are chronically addicted to alcohol and develops 48 hours after withdrawal from alcohol. This tremor is usually intact in persons who are not chronically addicted to alcohol and can be fatal (15%). Benzodiazepines can be significantly prolonged.

2. Seizures

   - Seizures appear only in persons who are chronically addicted to alcohol and occur intermittently, shouts at or tries to fend off hallucinated people or objects; hallucinations develop; psychogenic overactivity; tremulousness.

3. Delirium tremens

   - Severe psychological discomfort
   - Delirium tremens or delirium tremens than drugs cross tolerant with ethanol, and they can exacerbate seizures!

4. Intravenous ethanol infusions cannot be recommended.

Prevention of seizures and progression to DT antiepileptics (CARBAMAZEPINE, VALPROATE):

- Benzodiazepines can be significantly prolonged.
- Benzodiazepines may be administered for 5 days. The patient is jittery, HANGOVER (begins ≈ 8 hours after cessation of drinking, often after nights' sleep), hyperactivity of all sensory modalities (patient is jittery, startles easily, hyperreflexia, hypervigilance-insomnia), postural gross irregular (due to large amplitude), tremor of hands (can also cause titubation); tremor remits during relaxation and sleep, but often persists for weeks.

   - Promptly relieved by ethanol - many alcoholics view their so-called shakes as indication that it is time to resume drinking in order to avoid more severe complications of withdrawal (e.g. taking morning drink to “calm nerves”).
   - Tremor pathophysiology probably represents 2 lighted room, presence of family or friends, reassurance.

Clinical Features

1. Tremor/tremors - first and most common sign (begins ≈ 8 hours after cessation of drinking, often after nights’ sleep); hyperactivity of all sensory modalities (patient is jittery, startles easily, hyperreflexia, hypervigilance-insomnia), postural gross irregular (due to large amplitude), tremor of hands (can also cause titubation); tremor remits during relaxation and sleep, but often persists for weeks.

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2. Nausea and anorexia

3. Diaphoresis, tachycardia, systolic hypertension & orthostatic hypotension

4. Agitation, irritability and anxiety

5. Headache, malaise or weakness

6. Seizures

 Except for inattention and inability to recall fully events that occurred during bente- mentation is usually intact.

Treatment

- Well-lighted room, presence of family or friends, reassurance.
- Benzodiazepines.
- Thiamine 100 mg/d (IM → PO) for 3 days + multivitamins (“banana bag”), balanced diet. 
- Magnesium Sulfate to hypomagnesemic patients.

DELIRIUM TREMENS (SEVERE ALCOHOL WITHDRAWAL)

- Occurs only in persons who are chronically addicted to alcohol (for 5-15 years).
- Develops 48-96 hours after withdrawal from alcohol – later than other withdrawal syndromes!

1. Psychotic overactivity - gross tremulousness, agitation, hyperactivity, delusions, vivid hallucinations (visual, kinesthetic - patient picks at bed clothes or stares wildly about and intermittently shouts at or tries to fend off hallucinated people or objects; patient frequently imagines that he is back at work and attempts to perform some related activity).

2. Symptomatic hyperactivity (tachycardia, hypertension, fever*, hyperhidrosis, dilated pupils).

   - *Meningitis is included in differential diagnosis (until ruled out by CSF analysis)
   - Those who have had chronic period of drinking before cessation experience most severe form.
   - Subsides after 3-5 days of full-blown symptoms (some reports of cases lasting 4-5 weeks).
   - Unremitting, can be fatal.

- Meningitis can be fatal.

- Antiepileptics: see above.

Treatment in ICU:

- Search thoroughly for underlying disease (e.g. subdural hematoma, pneumonia, meningitis).
- Careful hydration & electrolyte balance (patients are susceptible to hyponatremesia, hypokalemia, hypoglycemia, hypovolemia).
- Diet & vitamins have no effect, but must be given to prevent other complications (e.g. thiamine).
- Cooling blanket or alcohol sponges.
- Patients are extremely suggestive and respond well to reassurance (they generally should not be restrained).

- For agitation – sedatives; specific cross-tolerance of sedative with ethanol is less important than in early abstinence. See above.

- Paradox: 10 mg IV → 5-40 mg every 5 minutes until calm → maintenance IV (or IM) 5 mg or more every 1-4 hours, prn.

REVIEW OF THIAMINE

- Thiamin deficiency is common in alcoholic patients and can be fatal. It is caused by malnutrition, malabsorption, and ethanol-induced malabsorption.

Benzodiazepines

- Atenolol 2 mg PO IV every 4 hours (PRN doses). Split the total into 4 scheduled doses a day. After 24 hours of adequate symptom management by PRN doses of lorazepam, calculate total lorazepam 2 mg PO IV every 4 hours for CIWA score ≥ 8.

- Monitor respiratory status (if risk of respiratory depression with benzodiazepines)

- After 24 hours of adequate symptom management by PRN doses of lorazepam, calculate total of the last 24 hours of PRN doses. Split the total into 4 scheduled doses and give every 6 hours over the next 24 hours.

- Taper lorazepam by 20% each day over the next 5 days.

- It is recommended that patient be on no more than 4 mg lorazepam daily at discharge to avoid risk of benzodiazepine withdrawal.

- Do not provide prescription for lorazepam for self-taper due to risk of combining with alcohol.

MINOR ALCOHOL WITHDRAWAL (“SHAKES”, HANGOVER): appears within few hours of stopping or decreasing alcohol consumption, occurs in anyone after brief but excessive drinking.

- Lasts 2-4 days (occasionally 1-2 weeks until full resolution).

- Beta-adrenergic blockers (dexamethasone, decrease agitation and autonomic signs)

*Examples of most commonly used agents:

- Benzodiazepines (e.g. Chlorazapexide, 25-100 mg IV or PO, repeated q6h as needed, max 500 mg in first 24 hours; Clonazepam, Diazepam 5-40 mg PO or IV q4h; Oxazepam [preferred in severe hepatic failure]; short acting - does not accumulate - does not contribute to excessive CNS depression).

- Short-acting benzodiazepines (lorazepam, oxazepam) are preferred for patients with significant liver disease because half-lives of other benzodiazepines can be significantly prolonged.

- Clomethiazole: see p. 33.

Examples of less commonly used agents:

- Barbiturates (e.g. PENTOBARBITAL 200 mg, PO, IM, or IV → 100 mg hourly prn).

- Paraldehyde 5-15 mg, PO or IV → repeated hourly prn.

Neuroleptics are less likely to prevent hallucinosis or delirium tremens than drugs cross tolerant with ethanol, and they can exacerbate seizures!

Intravenous ethanol infusions cannot be recommended.
ALCOHOL WITHDRAWAL SEIZURES ("RUM FITS")

- one or few brief, generalized tonic-clonic convulsions 4-6 hours after cessation of ethanol intake in small percentage (3.4%) of patients
- can occur in otherwise asymptomatic patients.
- due to kindling, with each episode of withdrawal seizure threshold lowers → risk and severity of seizures.
- interictal EEG is normal; marked sensitivity to photic stimulation during EEG.
- treatment is generally not required (isolated seizures are typically self-limited and not responsive to anticonvulsants) – IV DIAZEPAM for repeated seizures.

N.B. 30%-60% untreated patients progress to delirium tremens.
- outpatient PHENYTOIN is almost always waste of time and drug (because seizures occur only under stress of alcohol withdrawal, and patients who are withdrawing or heavily drinking do not take their anticonvulsants).

Seizures Precipitated by Alcohol
- focal seizures during alcoholic intoxication
- reflect intrinsic CNS lesion – patients require basic neurologic workup for seizure (interictal EEG shows focal slowing) and treatment with anticonvulsants.
- ethanol can precipitate seizures in any epileptic; most often postraumatic epilepsy due to multiple falls.

Persistent focal seizures in alcoholic are subdural hematoma unless proven otherwise.

ALCOHOL HALLUCINOSIS

(s. alcohol-induced psychotic disorder with hallucinations in DSM-IV)
- rare condition that develops within 48 hours of drinking cessation (or at end of long binge with gradual decreases in blood alcohol levels).

Principal symptom – vivid auditory hallucinations without gross confusion (at first, patients tend to accept voices as real and react accordingly, but as intensity of hallucinations wanes, patients recognize their illusion).
N.B. Patient is not disoriented, no autonomic instability – therefore does not have delirium tremens
- patient hears threatening or derogatory voices that discuss patient in third person or speak directly to patient.
- command hallucinations are absent.
- last few hours + days (in 10% cases may persist for months, may even become chronic – indistinguishable from schizophrenia).

Treatment – antipsychotic (e.g. RISPERIDONE, OLANZAPINE).

CHRONIC ALCOHOLISM (ALCOHOL ADDICTION, ALCOHOL DEPENDENCE)

Alcohol abuse or dependence usually develops during first 5 years of regular use of alcohol.

Patterns of chronic alcohol abuse
1. Regular daily excessive drinking.
2. Regular heavy drinking on weekends only.
3. Long periods of sobriety interspersed with binges that last days + months.

ALCOHOLISM - chronic, repetitive, excessive alcohol use that interferes with relationships, and livelihood of drinker.
- in pharmacological terms, alcoholism is addiction to alcohol.

DSM-IV-TR criteria for substance dependence → see p. Psy23 >>

ETIOLOGY

General plays major role in alcohol abuse (evidence supported by all kinds of studies – family, twin, adoption).
- identical twins have higher concordance for drinking behavior and possibly alcoholism, but environment determines which, if any, will manifest as alcoholics.
- whether reared by biologic or adoptive parents, sons of males with alcoholic problems are 4 times more likely to have problems with alcohol than sons of persons who are not (20% vs. 5%); daughters might be at increased risk if biological mother has alcoholism.
- children of alcoholic parents inherit higher tolerance.

Behavioral model: use LEARNING THEORY through operant conditioning, reinforcing elements of alcohol use become habitual.

Cognitive model: explain alcohol abuse in terms of “automatic thought”, which precede person’s more identifiable feelings about alcohol (e.g. automatic thought might be “I deserve drink because I’ve had rough day”).

Psychodynamic model: explain alcohol abuse in terms of ego defenses and intrapsychic conflicts - alcohol serves as way to escape uncomfortable internal conflict.

EPIDEMIOLOGY

Prevalence – 20% adult hospital patients (USA data); 6% patients in primary care offices (WHO data),  10% of general population.
- men: women = 2:1
  - women do not metabolize alcohol as efficiently as men.
  - problem drinking in women is much less common, onset occurs later, but progression is more rapid (females enter treatment earlier than males).
  - women more commonly combine alcohol with prescription drugs of abuse.
  - women are less likely to have job, financial, or legal troubles as result of drinking.
- following apply to US adult population:
  - Current drinkers - 44%
  - Former drinkers - 22%
Additional helpful screening questions:

1. Have you ever had drinking problem?
2. When was your last drink? (< 24 h is red flag.)
3. Do you use alcohol to relieve pain, anxiety, or insomnia?

If patient only asks questions on CAGE or AUDIT → craving for alcohol.

**AUDIT**

<table>
<thead>
<tr>
<th>Questions</th>
<th>0 Points</th>
<th>1 Point</th>
<th>2 Points</th>
<th>3 Points</th>
<th>4 Points</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. How often do you have drink containing alcohol?</td>
<td>Never</td>
<td>Monthly or less</td>
<td>2-4 times month</td>
<td>2-3 times week</td>
<td>4 times week</td>
</tr>
<tr>
<td>2. How many drinks containing alcohol do you have on typical day?</td>
<td>1 or 2</td>
<td>3 or 4</td>
<td>5 or 6</td>
<td>7/9</td>
<td>≥ 10</td>
</tr>
<tr>
<td>3. How often drink first thing in morning to steady your nerves or get rid of hangover?</td>
<td>Never</td>
<td>Less than monthly</td>
<td>Monthly</td>
<td>Weekly</td>
<td>(Almost) Daily</td>
</tr>
<tr>
<td>4. Have you ever felt need to cut down on your drinking?</td>
<td>No</td>
<td>Less than monthly</td>
<td>Monthly</td>
<td>Weekly</td>
<td>(Almost) Daily</td>
</tr>
<tr>
<td>5. Have you ever had drinking problem?</td>
<td>No</td>
<td>Less than monthly</td>
<td>Monthly</td>
<td>Weekly</td>
<td>(Almost) Daily</td>
</tr>
<tr>
<td>7. How often during past year have you found that you were not able to stop drinking once you had started?</td>
<td>Never</td>
<td>Less than monthly</td>
<td>Monthly</td>
<td>Weekly</td>
<td>(Almost) Daily</td>
</tr>
<tr>
<td>8. How often during past year have you been unable to remember what happened the night before because you had been drinking?</td>
<td>Never</td>
<td>Less than monthly</td>
<td>Monthly</td>
<td>Weekly</td>
<td>(Almost) Daily</td>
</tr>
<tr>
<td>9. Have you or has someone else been injured as result of your drinking?</td>
<td>No</td>
<td>Yes or not in past year</td>
<td>Yes, during past year</td>
<td></td>
<td></td>
</tr>
<tr>
<td>10. Have you ever had drinking problem?</td>
<td>No</td>
<td>Yes or not in past year</td>
<td>Yes, during past year</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**DIAGNOSIS**

**CAGE questionnaire** = [need to] cut down [on drinking], avoidance, guilt [about drinking], [need for] eye-opener.

- CAGE is best-known and most-studied short screening test for alcohol problems: easy to administer; sensitivity < 75%: *not adequate screening* for alcohol problems - may fail to identify binge drinkers, hazardous drinking.
- CAGE questions should be given face-to-face (not as paper and pencil test) and should be asked before questions on quantity and frequency (sensitivity of questions drops if quantity questions precede them).
- *Questions of CAGE:*
  1. Have you ever felt need to cut down on your drinking?
  2. Have people annoyed you by criticizing your drinking?
  3. Have you ever felt guilty about your drinking?
  4. Have you ever had drinking problem?

- *patients who answer affirmatively to 2 questions are 7 times more likely to be alcohol dependent than general population.*
- *patients who answer negatively to all 4 questions are 1/7 as likely to have alcoholism as general population.*
- CAGE.

**AUDIT questionnaire** = alcohol use disorders identification test.

- *best test for screening!!!*
- *can be administered as a paper and pencil test.*

**PATHOPHYSIOLOGY**

Opiate receptors are increased in brains (esp. nucleus accumbens) of recently abstinent alcoholic patients → craving for alcohol.

**HISTORY**

Diagnosis (esp. early diagnosis) is best made by history!!!

- *use term "person with alcohol problem" rather than "alcoholic".*
- *patients who answer affirmatively to 2 questions are 7 times more likely to be alcohol dependent than general population.*
- *patients who answer negatively to all 4 questions are 1/7 as likely to have alcoholism as general population.*
- CAGE.

**DIAGNOSIS**

**Additional helpful screening questions:**

1. Have you ever had drinking problem?
2. When was your last drink? (< 24 h is red flag.)
3. Do you use alcohol to relieve pain, anxiety, or insomnia?

**Risk factor:**

1. lower income and less educated groups.
2. Native Americans > Hispanic Americans > white Americans > African Americans, Asian Americans.
3. family history of alcoholism (esp. if individual is son of alcoholic father).
4. family history of tetanus (avoidance of alcohol under any circumstance).
5. alcoholic spouse.

**Lifestyle abstainers - 34%**

- Abuse and dependency in past year - 10% men and 4% women.
- Lifetime prevalence - 15% (20% men, 8% women) vs. 6% for other substances.
- prevalence declines with increasing age.
- alcoholism is more common in France than it is in Italy (despite virtually identical per capita alcohol consumption).

**DIAGNOSIS**

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- Abuse and dependency in past year - 10% men and 4% women.
- Lifetime prevalence - 15% (20% men, 8% women) vs. 6% for other substances.
Many physicians falsely believe no effective treatment is available for alcoholism. These physicians do not refer their patients for treatment.

**TREATMENT**

- complete abstinence is only treatment for alcohol dependence.

**CLASSIFICATION**

**Types of alcoholism:**

**Type 1**
1. (1) onset in adulthood (early twenties)
2. (2) drinking to relieve anxiety
3. (3) inherited but requires environmental trigger.

**Type 2**
1. (1) association with criminal behavior (sociopathy)
2. (2) onset in teen years
3. (3) drinking to get high.

- type 2 is associated with antisocial personality disorder.
- sons of persons with type 2 alcoholism are 7 times more likely to develop type 2 alcoholism compared with general population.

- presence of both serious, persistent mental illness and alcoholism is called DUAL DIAGNOSIS. Patients commonly use psychiatric disorder to deny alcohol abuse (only trial period of abstinence reliably distinguishes between primary alcoholism and alcohol abuse secondary to psychiatric condition).

- genetic psychiatric disorders are associated with alcoholism:
  1. schizophrenia
  2. bipolar disorder (risk 60%)
  3. depression, anxiety, antisocial personality all are more common in alcoholics than in general population (20.5% vs 7.2%, 23.5% vs 11.1%, and 18.3% vs 3.6%, respectively).

- of particular importance is common concurrence of posttraumatic stress disorder (PTSD) and alcohol abuse - activates symptoms of alcohol withdrawal aggregate PTSD = inevitable increased risk of relapse.
- alcohol abuse or dependence might reflect increased risk of relapse.
- bipolar manifold, insomnia).

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  3. depression, anxiety, antisocial personality all are more common in alcoholics than in general population (20.5% vs 7.2%, 23.5% vs 11.1%, and 18.3% vs 3.6%, respectively).

- of particular importance is common concurrence of posttraumatic stress disorder (PTSD) and alcohol abuse - activates symptoms of alcohol withdrawal aggregate PTSD = inevitable increased risk of relapse.
- alcohol abuse or dependence might reflect self-treatment for mental conditions (esp. panic disorder, generalized anxiety disorder, social phobia, dysthymic disorder, major depression, bipolar mania, insomnia).

- treating contributing problems aggressively (e.g., primary depression, anxiety disorder).

**DIAGNOSIS**

- compare medical supervision and PSYCHOTHERAPY.

- major obstacles to therapeutic success are denial of problem severity and wish to continue drinking.

- first step in treatment - physician states unequivocally that patient has problem with alcohol and emphasizes that this determination stems from consequences of alcohol in that patient's life, not from quantity of alcohol consumed.

- brief advice given early makes difference!
  - emphasize effects on family, friends, and occupation, as well as any physical manifestations.
  - be empathic and nonjudgmental.
  - avoid arguments about diagnosis.
  - indicate responsibility for change is with patient.
  - determine patient's readiness for change.
  - ask to bring family member to next appointment (involving family can be vital step on path toward recovery!)
  - suggest 2-week abstinence trial.
  - good strategy is to learn about patients' goals and indicate discrepancies between their goals and their choices.

- frequent follow-up is essential to support patient in recovery.

- N.B. treatment does not end with sobriety! Recovery means that patient can handle stresses of everyday life without alcohol! - most common mistake physicians make is assuming too soon that patient is stable.

- patient should be warned that after few weeks, when he has recovered from his last bout, he is likely to find excuse to drink.Patient may try controlled drinking for few days but he will most likely lose control eventually, so best approach is complete abstinence.

- patient must be able to do following:

- Perform urine toxic screen for other drugs of abuse!

- PHYSICAL EXAMINATION

- too low sensitivity?
  1. Liver function tests
  2. Mean corpuscular volume
  3. Gamma glutamyl transferase (best test, but even it has sensitivity only = 50%)
  4. Ethyl glucuronide (EtG) - metabolite of alcohol - can be detected in urine for up to 5 days after heavy binge drinking!
  5. Blood alcohol level indicates alcoholism with high degree of reliability if:
     a) > 300 mg/dL
     b) > 130 mg/dL, without gross evidence of intoxication
     c) > 100 mg/dL, upon routine examination

- MEDICAL SUPERVISION

- FRAMEWORK (involving family can be vital step on path toward recovery!)

- good strategy is to learn about patients' goals and indicate discrepancies between their goals and their choices.

- frequent follow-up is essential to support patient in recovery.

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- patient must be able to do following:

- Perform urine toxic screen for other drugs of abuse!
learn to say no to drinking in social situations (ask patient exactly what he is going to say and do when asked at parties what he wants to drink).
handle heavy-drinking friends who will try to undermine patient's sobriety.
handle stress (patients should not ignore symptoms of anxiety).
avoid boredom (prior to recovery, patients spent great deal of time drinking or recovering from drinking; upon abstinence, patients will have more free time).
learn to get along again with family and close friends (family problems often increase when drinking stops).
identify situations that can lead to drinking and develop ways to cope with them.
practice responses to these high-risk situations.
− patient should have list of phone numbers of people he can call when having difficult time coping (put list in convenient location because during high-stress periods they may become emotionally and mentally disoriented, necessitating written instructions).

5 stages of change (Prochaska) - fundamental guidance for enhancing motivation

1. Precontemplation phase - individual does not express any interest in need for change; many individuals with substance use problems are firmly entrenched in this stage.
2. Contemplation phase - first evidence of dynamic behavior - individual expresses tentative belief in possibility that alcohol use might be harmful; hallmark of this stage is ambivalence and vacillation (patient is receptive to new information, or just as likely reassured that current behavior is acceptable, in absence of information).
3. Preparation stage - clinician successfully alters balance in favor of healthy choice – it is thoughtfully focused on making plans.
4. Action stage - full recognition of problem along with observable evidence of steps taken to reduce alcohol use; patient should be given list of options for treatment including enrollment in AA and pharmacotherapy.
5. Maintenance stage - most mature stage - motivational efforts are directed toward maintaining hard won gains and preventing slips.

1. patients might be angry initially and storm out of office, but then patient might recall physician's warning months or years later and stop drinking.
2. if patient denies problem, recommending joining AA will not work.
3. patients might be angry initially and storm out of office, but then patient might recall physician's warning.
4. if patient has relapse or patients who recognize problem and will consider referral, cheapest (free) and most accessible option is AA.

Strongly recommend AA!
− when patient has urge to drink
  1) self-distraction (get involved with alternate activity to enjoy)
  2) thought stopping (do not dwell on thoughts of drinking but stop these thoughts)
  3) reprogramming (avoid activities that remind drinking)
  4) use of social support structure.
− if patient has relapse, find out what happened (make diagnosis) in order to formulate new treatment plan; patient must be actively involved in devising solutions (do not attempt to solve problem for patient!)
  − determine what patient thinks is appropriate treatment.
  − reinforce patient's decision to seek help.
  − emphasize that complete abstinence is only solution.
  − reframe relapse as learning opportunity.
  − provide support and empathy (reassure with encouragement such as "we can do this together").
  − have patient come up with ways to avoid triggering event.
  − have patient rehearse what to do in high-risk situations.

AA (Alcoholics Anonymous)

− success rate = 34%.
− physician should have AA literature in office (dates and places of meetings), have AA phone number available.
− AA groups also include high proportion of nonvoluntary enrollees (attendance mandated by court or probation officer order).
− AA 12-step approach involves psychosocial techniques used in changing behavior (e.g. rewards, relapse prevention, networks).
− each new person is assigned AA sponsor (person recovering from alcoholism who supervises and supports recovery of new member). Sponsors should be older and should be of same sex as patient (opposite sex if patient is homosexual).
  − AA provides patient with nondrinking friends who are always available and nondrinking environment in which to socialize.
  − patient hears others confess before group every rationalization he has ever used for his own drinking.
− help patient gives other alcoholics which may give him self-regard and confidence formerly found only in alcohol.
  − patients do not need strong religious background to be successful in AA; they only need belief in power higher than themselves.
  − urge patients to use aspects of program that can help them stay sober and ignore that are not helpful.
  − patients should try at least 5-10 different meetings before giving up on an AA approach because each meeting is different.
  − patients need to attend meetings regularly (daily at first) and for sufficient length of time (usually ≥ 2 yrs) because recovery is difficult and lengthy process.
  − in beginning (and perhaps ongoing) patients should remove alcohol from their homes and avoid bars and other establishments where strong pressures to drink may influence successful abstinence.

Tips
− alcoholics often have poor diet (folate deficiency is common!).
− advise to eat plenty of fruits and vegetables and consider multivitamin supplement.

Medications

1. Treatment of alcohol withdrawal - benzodiazepines (avoid fixed-dose therapy, and treat patients for symptoms). See also
  − β-blockers, clonidine, phenothiazines, anticonvulsants can be used with benzodiazepines.
2. Maintenance

Disulfiram (Antabuse) see also p. 702

− ibudil ALDEHYDE DEHYDROGENASE → ACETALDEHYDE accumulates.
− used as adjunct to counseling and AA with motivated patients to reduce risk of relapse.
− drinking alcohol within 12 h of taking disulfiram produces adverse effects - within 5-15 min:
  − warming up of face and chest, throbbing headache, nausea, vomiting, chest pain, palpitations, hypotension, sweating, dyspnea, anxiety, confusion, weakness, vertigo and blurred vision; reaction can last up to 5 h.
  − H: v. E. & antagonists - may abort alcohol-disulfiram reaction; severe reactions can be fatal (require hospital admission with management of hypotension and cardiac arrhythmia).
  − effects may persist for 3-7 days after last dose.
  − contraindications - severe myocardial disease, coronary occlusion, pregnancy.
− do not administer with METRONIDAZOLE.

Drugs
Alcohol affects virtually every organ system!

- Blocks GABA: receptor (primarily γ receptors) → decreased craving for alcohol.
- Patient must be abstinent for 5-7 d before beginning therapy.
- Also safe to give to patients who are still drinking - drug will gradually result in patient consuming less alcohol.
- Initially administered daily, later only with strong urge to drink (patients should carry NALTREXONE with them indefinitely).
- Always take NALTREXONE prior to drinking alcohol!
- FDA approved prolonged paternal form (Vivitrol) (≥ 1/month)
- N.B. naltrexone is most useful for patients who continue to sample alcohol (drug reduces relapse to heavy drinking)
- Adverse effects: nausea and/or vomiting, abdominal pain, sleepiness, nasal congestion.

NALTREXONE (Revia)
- Blocks GABA: receptors (µ, δ, κ receptors).
- Efficacy similar to naltrexone.

ACAMPROSATE (Campral)
- Blocks glutamate receptors, stimulates GABA transmission → restored neuronal excitation and inhibition balance.
- Chemical structure similar to homotaurine (structural analogue of GABA).
- Abstinence rates are doubled, but most patients return to drinking while still using drug.
- N.B. naltrexone is superior toacamprosate.
- Initiate ASAP after alcohol withdrawal when abstinence has been achieved.
- Adverse effect – diarrhoea.

TOBRIAMATE (facilitates GABA function and antagonizes glutamate) → decrease in mesocorticolimbic dopaminergic activity after alcohol (i.e. suitable for patient who still consumes alcohol) → reduced cravings.

Antidepressants - do not benefit patients who are not depressed.

**DIS**

- De Radder, Dirk MD et al "Anterior Cingulate Implant for Alcohol Dependence" Neurosurgery; April 13, 2016
- 2 "back-to-back" paddle electrodes were implanted for bilateral dorsal anterior cingulate cortex stimulation - using burst stimulation, quick improvement was obtained on craving, agoraphobia, and associated anxiety without expected withdrawal symptoms; patient has remained free of alcohol intake and relieved of agoraphobia and anxiety for over 15 months; patient perceives a mental freedom by not being constantly focused on alcohol.

**COMPLICATIONS (ALCOHOLISM CONSEQUENCES)**

Alcohol affects virtually every organ system (via nutritional deficiencies or direct toxic effect)

1. Malnutrition
2. Alcohol-related hepatitis & cirrhosis → glycogenostasis, testicular atrophy, impotence, spider angioma, hepatic encephalopathy ( asterixis, confusion, diffuse swelling with triphasic waves on EEG), nearly all cirrhosis deaths in people 45 yrs. are caused by ethanol.
3. Pancreatitis
4. Gastritis, peptic ulcer → GI bleeding
5. Cardiomyopathy, hypertension
7. Cerebral atrophy, Alcoholic Dementia - due to chronic excess alcohol ingestion.

- essential clinical features - combination of cognitive and behavioral deficits (impaired memory and judgment, loss of social refinements, paranoid ideation, etc.) - develop gradually and continue to progress as long as alcohol abuse continues.
- neuroimaging - shrinkage of cerebral volume (esp. frontal lobes) - potentially reversible if patients cease alcohol intake, but dementia tends to remain static.

8. Alcoholic Cerebellar Degeneration

- thiamine deficiency is suggested as cause (clinical and pathologic similarity to cerebellar component of Wernicke syndrome).
- progressive gait instability with widened base (unable to walk with one foot placed in front of other), trunk instability, up to frank ataxia of lower extremities (heel-to-shin test).
- upper limbs are only rarely involved.
- prominent nystagmus and dysarthria should suggest another cause for ataxia!
- neuromyelitis - atrophy of anterosuperior vermis.
- pathologic - neuron loss and gliosis in molecular, granular, and especially Purkinje cell layers.
- utility of vitamin supplementation after cerebellar degeneration has occurred is unproven.

Anterior vermian atrophy.

Source of picture: "WebPath - The Internet Pathology Laboratory for Medical Education" (by Laurel E. Klein, MD) >>

9. Denaturing disorders see p. Dem15 >>

1) central pontine myelinolysis
2) Marchiafava-Bignami disease

10. Myopathy - two forms:
1) acute necrotizing myopathy - swollen and tender one or more muscles, weakness, cramps, high creatine kinase, and rhabdomyolysis with or without myoglobinuria; type I fiber atrophy; resolve in days → weeks after abstaining, long-term disabilty is uncommon (unless repeated attacks)
2) chronic myopathy - painless (often unnoticed by patient), proximal weakness, type II fiber atrophy; associated cardiomyopathy.

- proposed mechanisms: ethanol toxicity; mitochondrial dysfunction, phosphorus and potassium depletion, rhabdomyolysis (induced by either alcohol-related seizures or limb compression from alcoholic stupor), acute myopathy may require additional insult (hyponkalemia, fasting, seizures, delirium tremens, prolonged limb compression).
- management: strict abstinence, IV saline diuresis (to prevent renal failure from myoglobinuria), thiamine and multivitamin supplementation.

11. Alcoholic Hypopyonemia, Alcoholic Keratoconjunctivitis see p. 2750 >>

- moderate consumption reduces risk of diabetes, but heavy alcohol consumption may increase risk.

12. Deficiency Anemias see p. Eye62 >>

13. Injuries & accidents (esp. automobile > ½ involve alcohol)
- thrombocytopenia (direct effect of ethanol and consequence of cirrhosis) + hypocoagulation → Risk of intracranial hematomas after head injury.
- close observation is essential after even mild head injury in intoxicated patients (unable to walk with one foot placed in at least ½ involve alcohol).

14. Suicide and Homicide
- 60-70% domestic violence incidents involve alcohol.
- alcohol is frequent component of many suicides (even in patients who are not alcoholic).

15. Sexual, marital, and legal problems

16. Depression

17. Dupuytren contractures

- alteration of WBC function contributes to predisposition to infection (e.g. bacterial or tuberculous meningitis).
- binge drinking significantly increases risk of injury and contracting STD.
- alcoholics lack sleep slow wave sleep, and have frequent arousals throughout night → impaired daytime alertness, sleep remains disturbed for years after discontinuance of alcohol usage.

ALCOHOLIC NEUROPATHY

- 9.30% hospitalized alcoholics, up to 93% ambulatory alcoholics have electroneurophysiological evidence.

1. nutritional deficiency (esp. B group vitamins, esp. thiamine).
2. direct toxic contribution of alcohol (altered membrane lipid permeability, oxidation injury from free radical formation) - no unequivical evidence!

Alcohols with neuropathy were allowed to continue drinking while with vitamin supplementation, and all noted improvement in symptoms if patients cease alcohol intake, but dementia tends to remain static.

ALCOHOLIC SYNDROMES

- bland "dying back" axonal degeneration affecting autonomic, sensory and motor fibers (virtually identical to beriberi due to thiamine deficiency).

CLINICAL FEATURES
Autonomic Neuropathy
- contributes to high mortality rates associated with alcoholism.
- pathologic changes in vagus nerves, sympathetic fibers, and ganglia.
- orthostatic hypotension may be prominent.
- impotence is major problem.
- urinary and fecal incontinence, hypotension, hypothermia, cardiac arrhythmia, dysphagia, dysphonia, impaired esophageal peristalsis, altered sweat patterns.
- pupillary parasympathetic denervation is rare.

Distal Polyneuropathy
Upper extremities are relatively spared!
- lost ankle ± knee reflexes!!!
- sensory symptoms - pain & paresthesias on soles (burning feet and severe hyperpathia*), exquisite tenderness of calves or soles, mild = moderate reduction of all sensory modalities (earliest - vibratory sense).
- distal lower limb weakness (may progress to wrist-drop and foot-drop).
- sensory ataxia may develop.
- skin over legs is thin, pigmented, shiny, subject to trauma and ulceration.
- neuropathic arthropathy of feet is common.

TREATMENT
1) nutrition (high-protein diet with B vitamin supplements).
2) abstinence from alcohol.
3) PHENYTOIN or CARBAMAZEPINE during acute stage.

in advanced cases, disease may progress for period after initiation of therapy, and recovery may be incomplete.

Peripheral nerve pressure palsies
- especially radial and peroneal nerves - intoxicated subjects tend to sleep deeply in unusual locations and positions.
- nutritional polyneuropathy increases vulnerability of peripheral nerves to compression injury.
- recovery takes days ÷ weeks (splints during this period can prevent contractures).

KORSAKOFF PSYCHOSIS
- intergrade and retrograde amnesia → confabulation, confusion.
- often preceded by untreated Wernicke encephalopathy (i.e. Korsakoff psychosis is chronic sequela of Wernicke encephalopathy).
- pathologically indistinguishable from Wernicke encephalopathy.
- largely irreversible.

WERNICKE ENCEPHALOPATHY
- Carl Wernicke (1881) called POLYENCEPHALITIS HEMORRHAGICA SUPERIORI.

ETYLOGY
- thiamine deficiency:
  a) heavy, long-term alcohol use - most commonly!
  b) persistent emesis
  c) starvation (anorexia nervosa, prisoners of war)
  d) total parental nutrition
  alcohol interferes with active GI transport; chronic liver disease → decreased activation of thiamine pyrophosphate from thiamine + decreased capacity of liver to store thiamine.
- genetic predisposition (e.g. abnormality of thiamine-dependent enzymes) plays role – not all malnourished alcoholics develop WE.

PATHOPHYSIOLOGY
- diffuse decrease in cerebral glucose utilization.
- dilated capillaries with prominent endothelial cells → macrofoci of hemorrhage and necrosis - symmetrically distributed around 3rd ventricle, aqueduct, and 4th ventricle (mamillary bodies, dorsomedial thalamus, locus ceruleus, periaqueductal gray matter, ocular motor nuclei, vestibular nuclei).
- cerebellar vermis and peripheral nerves are also damaged.

Small petechial hemorrhages in mammillary bodies.
No single finding is pathognomonic.

- Acute onset:
  1. Ataxia (wide-based, unsteady, shortened gait);
  2. Nystagmus (vertical and horizontal);
  3. Ataxia:
     - conjugate gaze palsy (horizontal and vertical);
     - nystagmus (vertical and horizontal);
     - nystagmus (vertical and horizontal and slow phase experience opposed direction).
- Moderate onset:
  1. Subacute alcoholic hallucinosis (such symptom complex is termed Wernicke-Korsakoff syndrome).
  2. Subacute alcoholic encephalopathy:
     - subacute alcoholic encephalopathy (such symptom complex is termed Wernicke-Korsakoff syndrome).
- Chronic onset:
  1. Wernicke encephalopathy is medical emergency
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     - IV glucose to severely malnourished patient can ex
  2. Wernicke encephalopathy is medical emergency
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  7. Wernicke encephalopathy is medical emergency
     - IV glucose to severely malnourished patient can ex
     - thiamine therapy).
- Diagnosis:
  - Recognition of underlying undernutrition or vitamin deficiency.
  - Instrumental/laboratory tests—only to exclude other etiologies.

**Coronal postcontrast T1**
- Abnormal enhancement of mammillary bodies (arrowhead), typical of acute Wernicke's encephalopathy.

**Clinical features**

- Acute onset:
  1. Ataxia (wide-based, unsteady, shortened gait);
  2. Nystagmus (vertical and horizontal);
  3. Ataxia:
     - conjugate gaze palsy (horizontal and vertical);
     - nystagmus (vertical and horizontal);
     - nystagmus (vertical and horizontal and slow phase experience opposed direction).

**Treatment**

Wernicke encephalopathy is medical emergency—untreated progresses to death.

- Early treatment can rapidly (within 24 h) reverse opthalmoplegia and improve ataxia.

*Failure of osmolar abnormalities to respond to thiamine in this manner should raise doubt as to veracity of diagnosis.

**IV thiamine** (50-100 mg) → daily 50-100 mg as IV, IM, or PO (GI absorption is impaired in chronic alcoholics!)

- Supplement electrolytes (60-180 mEq potassium, 10-50 mEq magnesium, 10-40 mmol/L phosphate) per day provide optimum metabolic balance.
- Magnesium is thiamine transketolase cofactor (hypomagnesemia → resistance to thiamine therapy).

**Supplement other vitamins**

- Always administer thiamine prior to IV glucose in patients at high risk for Wernicke-Korsakoff syndrome IV glucose to severely malnourished patient can exhaust thiamine supply → Wernicke-Korsakoff syndrome.

**Prognosis**

- Mortality in treated cases: 10-20% (infection, hepatic failure).
- Full recovery of ocular function occurs (vertical nystagmus may persist for months; fine horizontal nystagmus may be asymmetric in the superior and inferior portions).
- Patients with complete recovery from ataxia.
- Memory deficit (Korsakoff psychosis) usually is irreversible!!!

**Fetal alcohol syndrome**

- Most common drug-induced teratogenesis; leading cause of mental retardation! 10-20% cause of mild-to-moderate mental retardation are result of effects of alcohol in utero.

**Any amount of alcohol consumption during pregnancy is risky** (in one study, incidence of abnormalities did not increase until 45 mL/d of alcohol [3 drinks/day] was ingested).

**If mother-to-be does drink—advise to do so on full stomach (to minimize rapid rises in blood alcohol levels) + folate supplementation (may ameliorate risk of fetal malformations).**

- **Incidence:** 2.2 in 1000 live births (incidence exceeds Down syndrome and cerebral palsy!)
- **2-4% among children of alcohol-abusing women (> 30% of heavy drinkers)**
- **bunie drinking may be more important than chronic ethanol exposure; early gestation appears to be most vulnerable period.**
- **> 75% of all foster children in USA are of alcohol- or drug-dependent parents.**
- **Moderate alcohol consumption while pregnant → higher incidence of offspring problem drinking at age 21 years.**

**Clinical features**

- No single finding is pathognomonic.
- Each anomaly of syndrome may occur alone or in combination with others.
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<td>Hypotonia, poor coordination</td>
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<td>Hyperactivity, speech delay, learning</td>
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<td>disabilities (esp. arithmetic)</td>
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*midfacial hypoplasia (flat midface)

- lesser degrees of alcohol abuse result in less severe manifestations.
- mental retardation severity is related to severity of dysmorphogenesis.
- examine siblings for subtle manifestations of disorder.
- in families with several affected siblings, youngest child is usually most cognitively impaired.
- NEUROPSYCHIATRY: absence of corpus callosum, hydrocephalus, abnormal neuronal migration (cerebellar dysplasia, heterotopic, cell clusters).
- 1 in 6 babies born with this syndrome die.
- newborns may rarely exhibit withdrawal shortly after birth: restlessness, agitation, tremulousness, episotomous, seizures.
- maternal alcohol abuse is also associated with increased risk of spontaneous abortions, infant mortality, prematurity.
- alcohol transferred through breast milk - impairs motor development but not mental development at age 1 year; alcohol ingestion by children may lead to hypoglycemic seizures.
- infant treatment – good nutrition.

BIBLIOGRAPHY for ch. “Psychiatry” -> follow this LINK }