

Alcohol

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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, those 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 → 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:
 - nonspecific perturbation of neuronal membrane lipids.
 - action at interface between membrane lipids and integral membrane proteins.
 - direct action at neurotransmitter-gated ion channels (incl. acetylcholine, GABA_A, NMDA)

CATABOLISM

- mainly in liver - oxidized to **acetaldehyde** (via **ALCOHOL DEHYDROGENASE**) → **acetate** (via **ALDEHYDE DEHYDROGENASE**) → **CO₂** 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 (BEC falls 10-25 mg/dl/hour).
*i.e. constant rate without correlation to blood concentration
- 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 *INSULIN, AMINO ACIDS, FRUCTOSE*; starvation has opposite affect.

TOLERANCE

- 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 messengers* that serve to counteract short-term effects of alcohol.
- provides **CROSS-TOLERANCE** to many other CNS depressants (barbiturates, nonbarbiturate sedatives, benzodiazepines).

ALCOHOL INTOXICATION (DRUNKENNESS)

CLINICAL FEATURES

- 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) **anxiolysis & 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”.

PATHOLOGIC INTOXICATION - small dose of ethanol → sudden extreme excitement with irrational - violent behavior.

- probable mechanisms:
 - a) psychological dissociative reactions
 - b) paradoxical excitation (sometimes seen with barbiturate administration).
- delusions, hallucinations, and homicide may occur.
- episodes last minutes ÷ hours → sleep → amnesia for events.

Deepening intoxication:

- 1) **slurred speech**
- 2) **loss of coordination, unsteady gait**
- 3) **nystagmus, 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.

ALCOHOLIC 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).
- memory may be restored during later drinking bout.
- not associated with chronic memory disturbances.

- 2) **slow, noisy respiration, early respiratory depression**
- 3) **hypothermia**
- 4) **tachycardia**
- 5) **dilated pupils** (but may be normal in some)
- 6) **ICP↑**
- 7) **death** from **respiratory depression** (rare in absence of ingestion of additional substances, trauma, infection, or unconsciousness lasting > 12 hours).

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 imbibers, 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:

≈ 50 mg/dl	Sedation, tranquility
80 mg/dL	Legal driving limit in most USA states
50-150 mg/dl	Euphoria / dysphoria, shyness / expansiveness, friendliness / argumentativeness. Impaired concentration, judgment, sexual inhibitions
50-250 mg/dl	Slurred speech, ataxic gait, diplopia, nausea, tachycardia, drowsiness, labile mood (sudden bursts of anger, antisocial acts), delirium
300 mg/dl	Stupor alternates with combativeness or incoherent speech, heavy breathing, vomiting
400 mg/dl	Coma (death has occurred)
500 mg/dl	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 rises osmolality 22 mOsm/L 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. Meningitis

TREATMENT

- depends on level of consciousness:

Conscious patient needs little treatment beyond waiting for alcohol to be metabolized.

- avoid analeptics (ETHAMIVAN, CAFFEINE, AMPHETAMINE) - do not hasten sobriety + can cause *seizures* and *cardiac arrhythmia!*
- only practical agent that might accelerate ethanol elimination is **FRUCTOSE** (but causes GI upset, lactic acidosis, and osmotic diuresis).
- although patients are often depleted of magnesium, **MAGNESIUM SULFATE** may further depress sensorium.
- for **agitation**:
 - isolation, calming environment, reassurance.
 - **restraint** (safer than tranquilizers or sedatives - may potentiate CNS depressant effects of alcohol!).
 - low doses of high-potency **antipsychotics** (e.g. **HALOPERIDOL IV**, **RISPERIDONE** or **OLANZAPINE PO**) decrease hyperactivity without increasing sedation.

Stuporous or unconscious patient (generally managed similarly to poisoning by other depressant drugs; most important problem is *respiratory depression*)

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** (when necessary), prevent **aspiration**.
- **keep warm** with **legs elevated**.
- monitor BP, correct hypovolemia & acid-base imbalance (ketoacidosis is possible)
- hypoglycemia is possible; if serum glucose in doubt → IV 50% **GLUCOSE** with parenteral **THIAMINE**.
- for ICP↑ - **MANNITOL**, **corticosteroids**.
- in **extreme situations** (apneic 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** → ↑threshold to sleep induction, but synergistic interaction then increases depth and length of anesthetic stage reached.
- repeatedly used ethanol and **MORPHINE** can increase each other's potency.
- **mild disulfiram reaction** occurs in combination ethanol with **sulfonyleas** (e.g. **TOLBUTAMIDE**) or with some **antibiotics** (**CHLORAMPHENICOL**, **GRISEOFULVIN**, **ISONIAZID**, **METRONIDAZOLE**), **QUINACRINE**.

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 profound suppression** (may relate to GABA 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

- called “detoxification”.

Administer **sedative*** *with cross-tolerance with ethanol* in **loading dose to cause mild intoxication** (calming, dysarthria, ataxia, fine nystagmus); after 1-2 days, dosage is **gradually tapered** over 2-3 days with daily doses tapered by about one-fourth of preceding day's (with reinstatement of intoxicating doses should withdrawal symptoms reappear).

+ **β-adrenergic blockers** (dampen tremor, decrease agitation and autonomic signs)

*examples:

- benzodiazepines** (e.g. **CHLORDIAZEPOXIDE** 25-100 mg IV or PO, repeated q2-6h as needed, max 500 mg in first 24 hours; **CLORAZEPATE**; **DIAZEPAM** 5-40 mg PO or IV q1h; **OXAZEPAM** [preferred in severe hepatic failure; short acting - does not accumulate - does not contribute to excessive CNS depression])
shorter-acting benzodiazepines (LORAZEPAM, OXAZEPAM) are preferred for patients with significant liver disease because half-lives of other benzodiazepines can be significantly prolonged.
- barbiturates** (e.g. **PENTOBARBITAL** 200 mg, PO, IM, or IV → 100 mg hourly prn).
see p. Psy23 >>
- PARALDEHYDE** 5-15 mg, PO or PR → 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.

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).

Clinical Features

- Tremulousness** - first and most common sign (begins ≈ 8 hours after cessation of drinking, often after night's sleep): **hyperacuity of all sensory modalities** (patient is jittery, startles easily, hyperreflexia, hypervigilance-insomnia), **postural gross irregular 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. take morning drink to "calm nerves").
 - tremor pathophysiology probably represents **exaggerated physiological tremor**.
- Nausea and anorexia**
- Diaphoresis, tachycardia, systolic hypertension & orthostatic hypotension**
- Agitation, irritability and anxiety**
- Headache, malaise or weakness**
- Seizures**
- Except for inattentiveness and inability to recall fully events that occurred during binge, **mentation is usually intact**.

Treatment

- well-lighted room, presence of family or friends, reassurance.
- benzodiazepine**. *see above >>*
- THIAMINE** 100 mg/d (IM → PO) for 3 days; multivitamins, 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!

- Psychic 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).
- Sympathetic 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).
- untreated, **can be fatal (15%) due to autonomic dysfunction!**

Treatment - in ICU:

- search thoroughly for underlying disease (e.g. subdural hematoma, pneumonia, meningitis).
- careful **hydration & electrolyte balance** (patients are susceptible to hypomagnesemia, hypokalemia, hypoglycemia, hypovolemia).
- diet & vitamins** have no effect, but must be given to prevent other complications (esp. **THIAMINE** for 3-5 days).
- cooling blanket or alcohol sponges.
- patients are extremely suggestible 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 >>*
e.g. **DIAZEPAM** 10 mg IV → 5-40 mg every 5 minutes until calming → maintenance IV (or IM) 5 mg or more every 1-4 hours, prn.

N.B. required doses might be fatal in normal person!

for severe agitation, psychosis – HALOPERIDOL, RISPERIDONE.

- for central noradrenergic overactivity** – **CLONIDINE** (0.1 mg PO qid, increased gradually to 0.2-0.4 mg qid), **ATENOLOL** (50-100 mg PO qd); avoid hypotension!
- no evidence that steroids are of benefit.

ALCOHOL WITHDRAWAL SEIZURES ("RUM FITS")

- one or few **brief, generalized tonic-clonic convulsions 6-48 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 notoriously **unresponsive to anticonvulsants!**) - IV **DIAZEPAM** for repeated seizures.
 - N.B. 30-40% 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 posttraumatic epilepsy due to multiple falls.

Persistently focal seizures in alcoholic are **subdural hematoma** until 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 true origin).

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, even may 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 health, personal relationships, and livelihood of drinker.

- in pharmacological terms, alcoholism is **addiction to alcohol**.

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

ETIOLOGY

Genetics 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 models use **LEARNING THEORY**: through **operant conditioning**, reinforcing elements of alcohol use become habitual.

Cognitive models explain alcohol abuse in terms of "**automatic thoughts**", which precede person's more identifiable feelings about alcohol (e.g. automatic thought might be "I deserve drink because I've had rough day").

Psychoanalytic models 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%
 - Lifetime abstainers - 34%
 - Abuse and dependency in past year - 10% men and 4% women.
 - Lifetime prevalence - 13% (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).

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 teetotalism (avoidance of alcohol under any circumstance)
- 5) alcoholic spouse.

PATHOPHYSIOLOGY

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

DIAGNOSIS

HISTORY

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

- use term "person with alcohol problem" rather than "alcoholic".
- patients *frequently deny* they have problem (they might not link alcohol with its consequences + they might fear being reported to their employers).
- **diagnostic clues** to alcoholism:
 1. Inability to decrease or discontinue drinking.
 2. Binges lasting at least 2 days.
 3. Occasional consumption of fifth of spirits or equivalent in wine or beer in single day.
 4. Blackouts.
 5. Continued drinking despite physical illness that is exacerbated or caused by drinking.
 6. Drinking nonbeverage alcohol (e.g. shaving lotion).
 7. Drinking in morning.
 8. Withdrawal syndromes.
 9. Apparent sobriety in presence of elevated alcohol level in blood, indicating tolerance to sedative effects of alcohol.
 10. Arrest for DUI (driving under influence).

Screening for alcoholism:

- most commonly asked question by doctors "How much do you drink?" has < 50% sensitivity for alcohol problems.

CAGE questionnaire = [need to] cut down [on drinking], annoyance, 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 **C**ut down on your drinking?
 2. Have people **A**nnoyed you by criticizing your drinking?
 3. Have you ever felt **G**uilty about your drinking?
 4. Have you ever had drink first thing in morning to steady your nerves or get rid of hangover? (**E**ye-opener)
- 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 paper-and-pencil test.

Questions	0 Points	1 Point	2 Points	3 Points	4 Points
1. How often do you have drink containing alcohol?	Never	Monthly or less	2-4 times month	2-3 times week	≥ 4 times week
2. How many drinks containing alcohol do you have on typical day when you are drinking?	1 or 2	3 or 4	5 or 6	7-9	≥ 10
3. How often do you have 6 or more drinks on 1 occasion?	Never	Less than monthly	Monthly	Weekly	(Almost) Daily
4. How often during past year have you found that you were not able to stop drinking once you had started?	Never	Less than monthly	Monthly	Weekly	(Almost) Daily
5. How often during past year have you failed to do what was normally expected of you because of drinking?	Never	Less than monthly	Monthly	Weekly	(Almost) Daily
6. How often during past year have you needed first drink in morning to get yourself going after heavy drinking session?	Never	Less than monthly	Monthly	Weekly	(Almost) Daily
7. How often during past year have you had feeling of guilt or remorse after drinking?	Never	Less than monthly	Monthly	Weekly	(Almost) Daily
8. How often during past year have you been unable to remember what happened night before because you had been drinking?	Never	Less than monthly	Monthly	Weekly	(Almost) Daily
9. Have you or has someone else been injured as result of your drinking?	No		Yes, but not in past year		Yes, during past year
10. Has relative, friend, or doctor or other health care worker been concerned about your drinking or suggested you cut down?	No		Yes, but not in past year		Yes, during past year

If patient affirmatively answers questions on CAGE or AUDIT → **additional questions** about consequences of alcohol abuse patient has experienced (because diagnosis of alcohol dependence relies more on *consequences* of alcohol use and less on *amount* of alcohol consumed).

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?
4. Have you ever been arrested for drinking, such as driving under influence?
5. Have you ever lost friends or girlfriends/boyfriends because of your drinking?
6. Have you ever been to Alcoholics Anonymous (AA) meeting?

Additional questions specific to GERIATRIC population:

1. Did your drinking increase after someone close to you died?
2. Does alcohol make you sleepy so that you often fall asleep in your chair?

Additional questions specific to ADOLESCENT population:

1. Do you drink alone?
2. Do you ever miss school to go drinking or because you have hangover?

PHYSICAL EXAMINATION

- detects only consequences of alcoholism.

LABORATORY TESTS

- too low sensitivity!

1. **Liver function tests**
2. **Mean corpuscular volume**
3. **Gamma glutamyl transferase** (best test, but even it has sensitivity only $\approx 50\%$)
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) > 150 mg/dL without gross evidence of intoxication
 - c) > 100 mg/dL upon routine examination

Perform urine toxic screen for other drugs of abuse!

DIFFERENTIAL DIAGNOSIS

- 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%).
- 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** - activating symptoms of alcohol withdrawal aggravate PTSD \rightarrow inevitably 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).

CLASSIFICATION

Types of MALE alcoholism:

Type 1:

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

Type 2:

- (1) association with criminal behavior (sociopathy)
- (2) onset in teen years
- (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.

TREATMENT

also see p. Psy23 >>

Many physicians falsely believe no effective treatment is available for alcoholism - these physicians do not refer their patients for treatment.

Treatment is effective!

Complete abstinence is only treatment for alcohol dependence!
 - no evidence that alcoholics can resume controllable social drinking!

- treat contributory problems aggressively (e.g. primary depression, anxiety disorder).

REHABILITATION PROGRAMS

- combine **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:
 - 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 disorientated, necessitating written instructions).

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

N.B. stages of change represent cycle permitting both forward and backward movement!

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 skepticism (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 thoughtful phase 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 AA and pharmacotherapy.
 5. **Maintenance stage** - most mature stage - motivational efforts are directed toward promoting hard won gains and preventing slips.
- patient might be angry initially and storm out of office, but then patient might recall physician's warning months or years later and stop drinking.
 - if patient denies problem, recommending joining AA will not work.
 - for 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.
 - 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, social support networks, role models).
- each new person is **assigned AA sponsor** (person recovering from alcoholism who supervises and supports recovery of new member); sponsor 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 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 aspects that are not helpful.
- patients should try at least 5-10 different meetings before giving up on 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.

DIET

- 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 above >>*
 - β-blockers, clonidine, phenothiazines, anticonvulsants can be used with benzodiazepines.
2. **Maintenance**

DISULFIRAM (Antabuse) also see p. 702 >>

- **inhibits 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 minutes: warmth and flushing of face and chest, throbbing headache, nausea, vomiting, chest pain, palpitations, hypotension, sweating, dysphoria, anxiety, confusion, weakness, vertigo, and blurred vision; reaction can last up to 3 h.
H: **vit. C & antihistamines** - 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.
- studies found – DISULFIRAM decreases number of drinking days but does not increase abstinence.

NALTREXONE (ReVia) also see p. S21 >>

- **blocks OPIATE RECEPTORS** (primarily μ 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 parenteral form (Vivitrol) ($\times 1$ / 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.

NALMEFENE also see p. S21 >>

- **blocks OPIATE 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!
- initiate ASAP after alcohol withdrawal when abstinence has been achieved.
- adverse effect - diarrhea.

TOPIRAMATE facilitates GABA function and antagonizes GLUTAMATE → **decrease in mesocorticolimbic DOPAMINE** after alcohol (i.e. suitable for patient who still consumes alcohol) → reduced cravings.

Antidepressants - do not benefit patients who are not depressed.

PROGNOSIS

Amount of alcohol associated with lowest mortality:

2 drinks / day in men;

≤ 1 drink / day in women.

ABSTINENCE

- < 20% patients remain abstinent for full year.
- if has been sober for 2 years, relapse rate is 40%.
- if has been sober for 5 years, likely to remain sober, but they are still at risk for relapse
N.B. abstinence for < 5-6 years does not predict continued abstinence.
- **30% alcoholics stop drinking!**
- if patient has *serious psychopathology* (e.g. severe problems with family, peers, school, and police before age 15 y and before onset of alcohol problems), recovery is less likely.

CARDIOVASCULAR EFFECTS

- **moderate consumption (1-2 drinks/d)** reduces risk of cardiovascular disease (MI, stroke) in men and women by 30%.
 - cardiovascular benefit becomes important in men > 40 years and in women > 50 years.
 - no benefits for people at low risk for coronary disease (men < 40 y, women < 50 y).
- effect of **heavy alcohol consumption** on cardiovascular risk varies by drinking pattern:
 - drinking with meals* may reduce risk;
 - binge drinking* increases risk.
- risk of **hypertension** is increased with ≥ 3 drinks daily.

MORBIDITY & MORTALITY

Alcohol use is **3rd leading cause of preventable death in USA** (after smoking and obesity).

- 4% of global burden of disease is attributable to alcohol (7% in North America, Europe, Japan, Australia; 12% in Eastern Europe and Central Asia).
- alcohol is responsible for percentage of:
 - 1) cirrhosis - 32%
 - 2) esophageal cancer - 29%
 - 3) liver cancer - 25%
 - 4) homicides - 24%
 - 5) motor vehicle accidents - 20%
 - 6) mouth and oropharyngeal cancers - 19%
 - 7) suicides - 11%
 - 8) hemorrhagic stroke - 10%
 - 9) breast cancer - 7%
- morbidity & mortality is strongly related to **smoking** (people who drink heavily are less likely to quit smoking).

COMPLICATIONS (ALCOHOLISM CONSEQUENCES)

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

1. **Malnutrition**
2. **Alcohol-related hepatitis & cirrhosis** → gynecomastia, testicular atrophy, impotence, spider angiomas, hepatic encephalopathy (asterixis, confusion, diffuse slowing 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**
6. **Cancers**: breast, esophageal, liver.
7. **Cerebral atrophy, Alcoholic Dementia** - due to chronic excess alcohol ingestion.

N.B. notion that alcohol has direct toxic effect on cerebral tissue is greatly disputed - most cases of dementia can be explained on basis of Korsakoff's disease, other nutritional deficiencies, or medical causes; in animals, enormous doses of ethanol are required to produce morphologic changes in brain neurons.

- 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!
- **neuroimaging** – **atrophy of anterosuperior vermis**.
- **pathology**: 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 Edward C. Klatt, MD) >>

- Demyelinating disorders**: see p. Dem13 >>
 - 1) **central pontine myelinolysis**
 - 2) **Marchiafava-Bignami disease**
 - 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 disability 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 (hypokalemia, fasting, seizures, delirium tremens, prolonged limb compression).
 - **management**: strict abstinence, IVI saline diuresis (to prevent renal failure from myoglobinuria), thiamine and multivitamin supplementation.
 - Alcoholic Hypoglycemia, Alcoholic Ketoacidosis** see p. 2750 >>
 - moderate consumption reduces risk of **diabetes**, but heavy alcohol consumption may increase risk.
 - Deficiency Amblyopia** see p. Eye62 >>
 - 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 (abnormal sensorium must not be dismissed as drunkenness).
 - Suicide and Homicide**
 - 60-70% domestic violence incidents involve alcohol.
 - alcohol is frequent component of many suicides (even in patients who are not alcoholic).
 - Sexual, marital, and legal problems
 - Depression
 - 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 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 electrophysiological evidence.

ETIOLOGY

- 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 unequivocal evidence!

Alcoholics with neuropathy were allowed to continue drinking while receiving nutritious diet with vitamin supplementation, and all noted improvement in symptoms
- polyneuropathy and Wernicke's syndrome often occur in same patient.

PATHOLOGY

- 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).

*bed covers touching feet are painful

- 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

- **anterograde and retrograde amnesia** → confabulation, confusion. further see p. S6 >>
- 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 *POLIOENCEPHALITIS HEMORRHAGICA SUPERIORIS*.

ETIOLOGY

- **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:



Source of picture: "WebPath - The Internet Pathology Laboratory for Medical Education" (by Edward C. Klatt, MD) >>



Wernicke's encephalopathy. Wall of third ventricle is discolored and there are many small hemorrhages.

CLINICAL FEATURES

- acute onset:

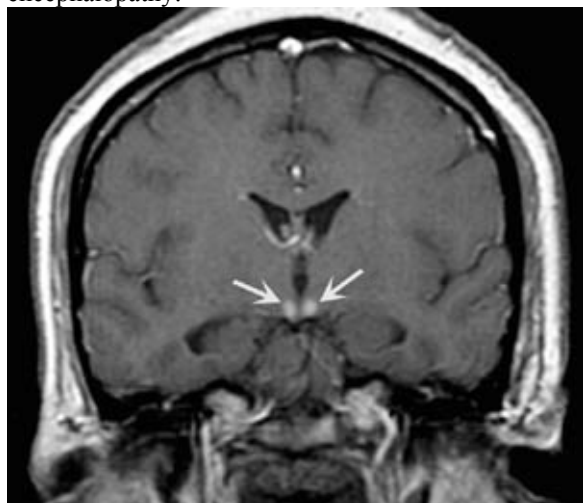
1. **Ataxia** (wide-based, uncertain short-stepped gait);
 - neuron loss in **superior vermis**; degeneration of all layers of cortex (esp. Purkinje cells).
 - **vestibular apparatus** also is affected (impaired oculovestibular reflex).
 - mildest form evident on tandem walking only.
 - most severe form - inability to stand / walk without assistance.
2. **Ophthalmoplegia** (usually lateral gaze palsy) - lesions in abducens nuclei and eye movement centers in pons and midbrain.
 - no significant neuron destruction (rapid improvement with thiamine repletion).
 - following abnormalities can occur singly or in combination:
 - 1) nystagmus (vertical and horizontal).
 - 2) lateral rectus palsy – bilateral, can be asymmetric.
 - 3) conjugate gaze palsy (horizontal ± vertical).
 - 4) nonreacting miotic pupils and complete ophthalmoplegia (in advanced cases).

- 5) ptosis, small retinal hemorrhages, involvement of near-far focusing mechanism, optic neuropathy (occasionally).
 - 6) papilledema (very rare).
3. **Quiet global confusional state** - profoundly disoriented, indifferent, and inattentive;
- with treatment, largely **irreversible Korsakoff amnesic syndrome** may become apparent (such symptom complex is termed **Wernicke-Korsakoff syndrome**).
- associated peripheral neuropathy is found in 80% patients.

DIAGNOSIS

- recognition of underlying undernutrition or vitamin deficiency.
- instrumental / laboratory tests – only to exclude other etiologies.

Coronal postcontrast T1-MRI - abnormal enhancement of mammillary bodies (*arrows*), typical of acute Wernicke's encephalopathy:



TREATMENT

- Wernicke encephalopathy is medical emergency - untreated progresses to death!
- early treatment can rapidly (within 24 h*) reverse ophthalmoplegia and improve ataxia!
 - *failure of ocular 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**, 10-30 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 persist indefinitely in 35-60% patients).
- 40% patients have 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% cases 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)
- **binge 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.



System	Majority	Minority
CNS	Mental retardation (may be severe) Microcephaly (due to brain growth↓) Hypotonia, poor coordination Hyperactivity, speech delay, learning disabilities (esp. arithmetic)	
Impaired growth	Prenatal & postnatal Diminished adipose tissue	
Eyes	Short palpebral fissures	Ptosis, epicanthal folds, blepharophimosis Strabismus Myopia Microphthalmia Cataracts Retinal pigmentary abnormalities

Nose	Short, upturned Long, smooth (hypoplastic) philtrum*	
Mouth	Thin vermilion lip borders Retrognathia in infancy Micrognathia* or prognathia in adolescence	Prominent lateral palatine ridges Cleft lip or palate Small teeth with faulty enamel
Maxilla	Hypoplastic*	
Ears		Posteriorly rotated Poorly formed concha
Skeletal		Klippel-Feil anomaly Scoliosis Pectus excavatum or carinatum Bifid xiphoid Radiolunar synostosis Syndactyly, clinodactyly, camptodactyly Nail hypoplasia Joint contractures
Cardiac		Septal defects Great vessel anomalies
Cutaneous		Abnormal palmar creases Hemangiomas Infantile hirsutism
Muscular		Hernias (diaphragmatic, inguinal, umbilical) Diastasis recti
Urogenital		Labial hypoplasia, hypospadias Small rotated kidneys, hydronephrosis

*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.
- NEUROPATHOLOGY: 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, opisthotonus, 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 >>](#)