Acentra HEALTH

Substance Use Disorders Withdrawal Management

Talk No. 1 | Alcohol

J. Mitchell Simson MD, MPH, FASAM

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Classes of Substances

This series of talks will review the withdrawal management for several classes of substances including:

ALCOHOL

OPIOIDS

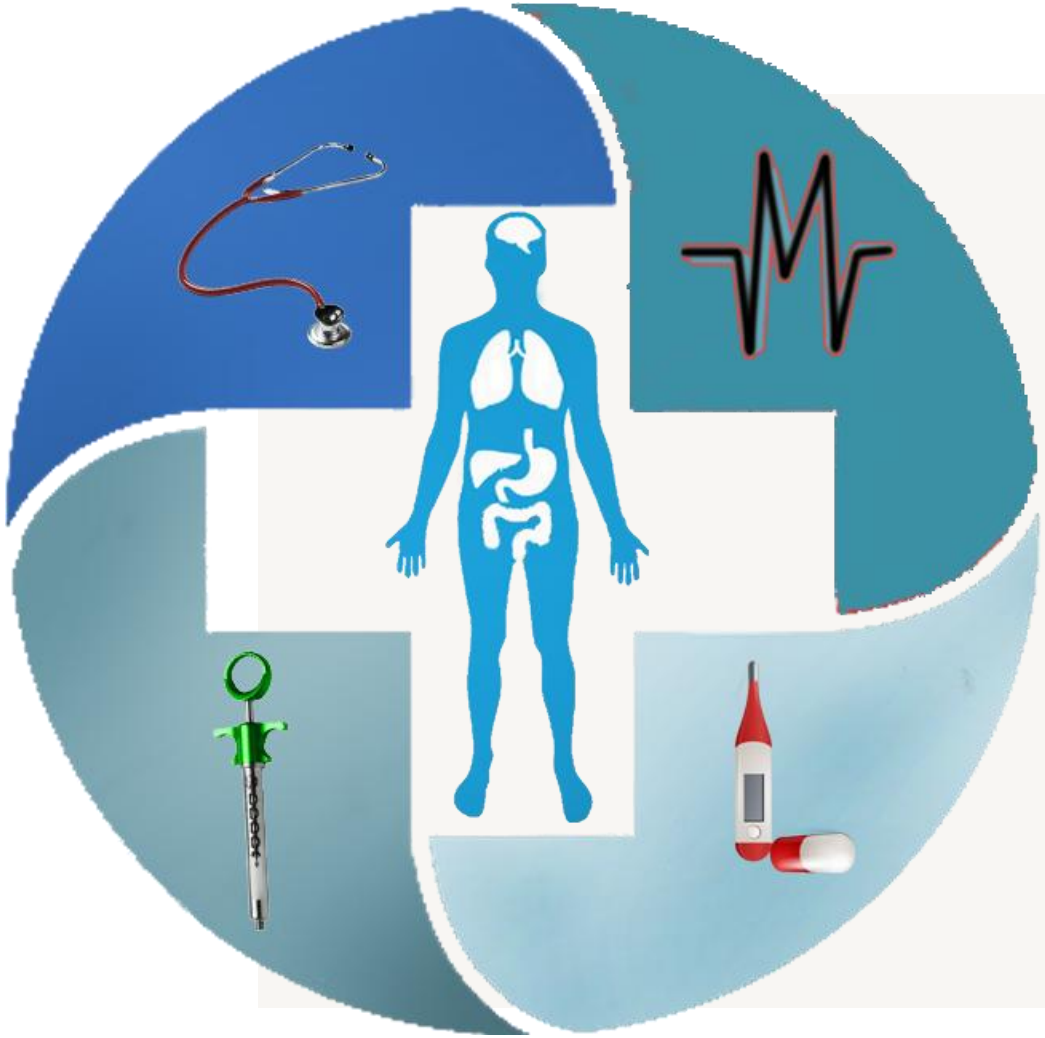
STIMULANTS

MARIJUANA

SEDATIVE / HYPNOTICS

OTHER REQUESTED SUBSTANCES

WM Classes of Substances Review Specifics



Within each class, I will review

- Historical perspectives
- Therapeutic uses and misuses
- Pharmacokinetics and mechanisms of action
- Acute and chronic toxicities
- Interventions for withdrawal management

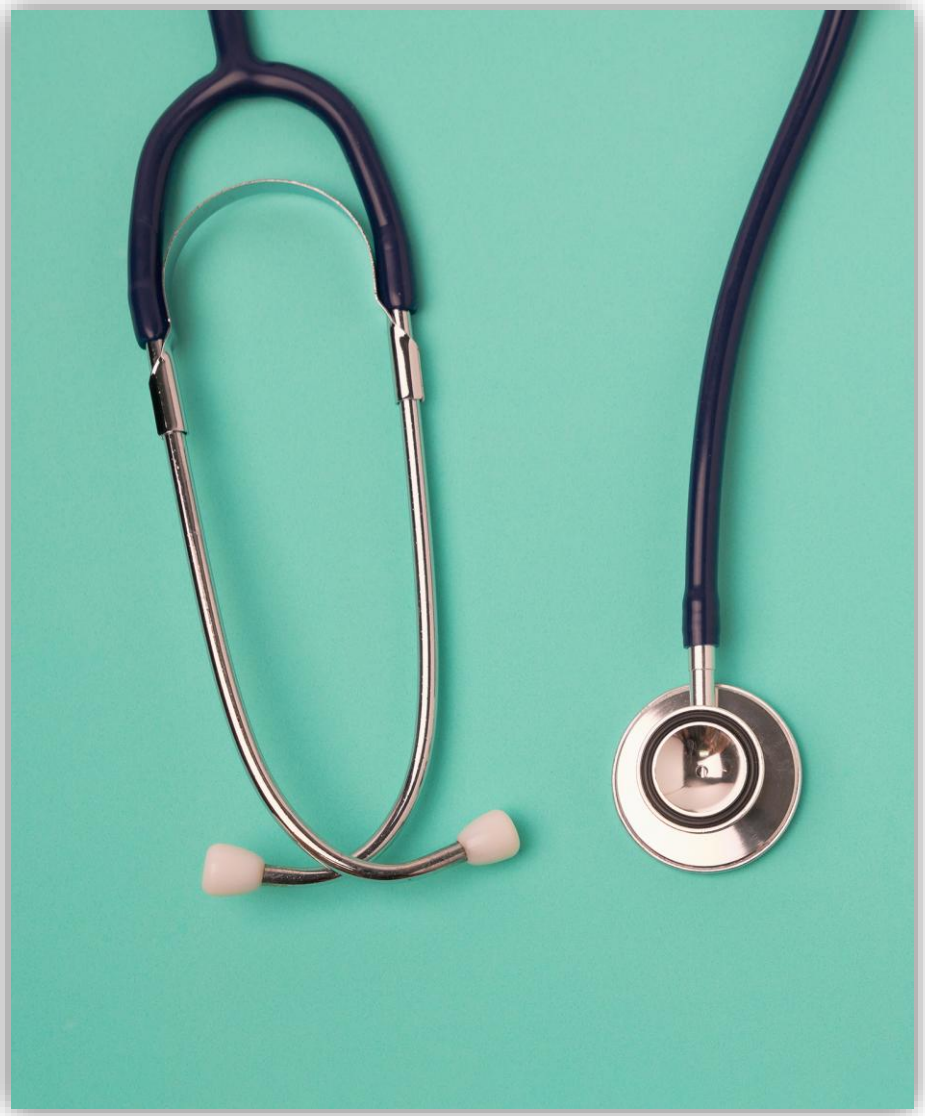
Q & A

Please submit questions during the talk.

Please include topics of interests for future talks on your evaluations.

Disclosures

- I am a Medical Director reviewer for Acentra
- I will be discussing off-label use of pharmaceuticals
- I am planning on enjoying myself and I hope you do as well



Definition

(Alcohol) From the medieval Latin

(Arabic) *al-kohl “the fine powder used to stain the eyelids”*

By extension to liquids the essence, quintessence, or ‘spirit’ obtained by distillation

Ethyl Alcohol

Ethyl alcohol comes in a variety of strengths (0.5%-50%, 1-100 proof), colors, flavors and packaging

THERAPEUTIC USES

Excellent solvent used as a vehicle in “elixirs”

Topical disinfectant—Covid!!

Topically reduces fever due to rapid evaporation on skin

Injected into nerves, such as for trigeminal neuralgia

Treatment of methanol and ethylene glycol poisoning

Delay premature labor

ABSORPTION, METABOLISM, MECHANISM OF ACTION

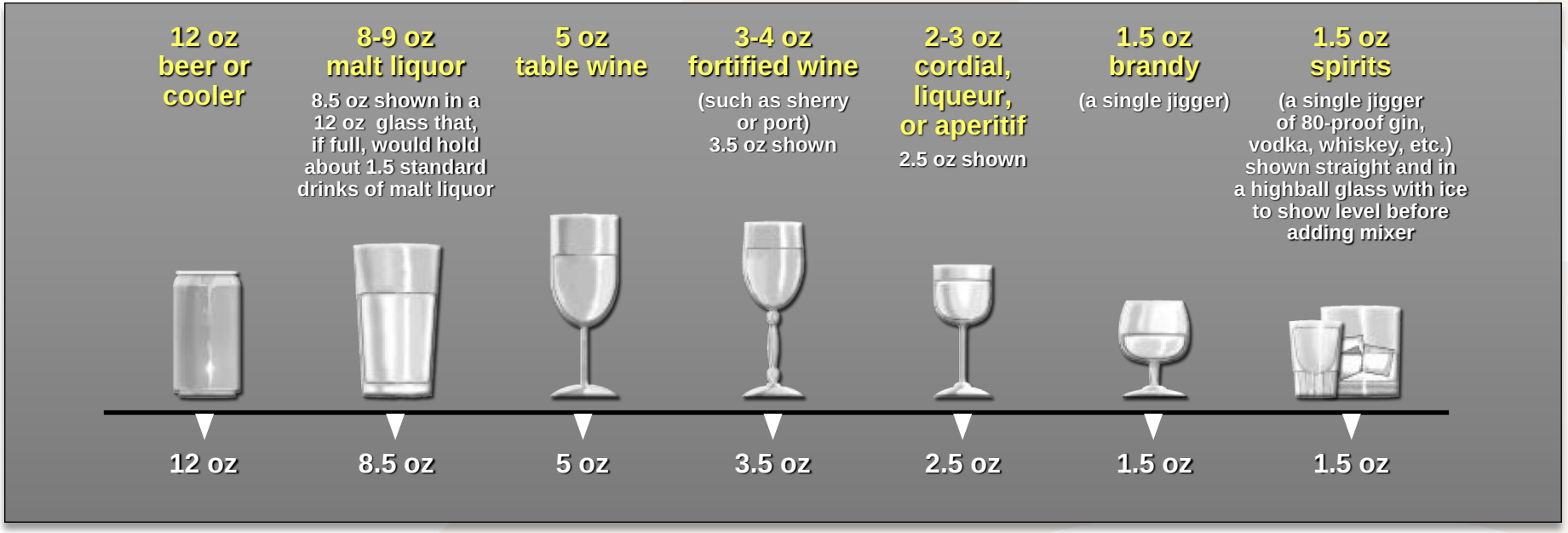
- Oral, topical, sterile injection
- Effects are dependent upon concentration of alcohol in the blood (BAC)
- Absorbed rapidly and efficiently from stomach, small intestine, colon
- Rate of absorption dependent upon gastric emptying time (reduced with carbonation) and gender
- Metabolized primarily in liver (some gastric—women have less of this) by alcohol dehydrogenase (ALD)
- *Thus women have a 20-25% higher BAC/same dose*
- Some metabolism by mixed function oxidases like P450IIE1 (CYP2E1)

ABSORPTION, METABOLISM, MECHANISM OF ACTION

- Rate of metabolism:
  - relatively constant,
  - proportional to body weight,
  - about 1 oz pure alcohol/3 hours OR
  - about one 12 oz. beer/hour
- Metabolized to acetaldehyde then converted to acetate by acetaldehyde dehydrogenase (ALDH) and then used as energy source or stored
- Rapid distribution to all tissues in body including fetus in pregnancy
- No amethystic agents (alcohol antagonists)

Defining the “Standard Drink”

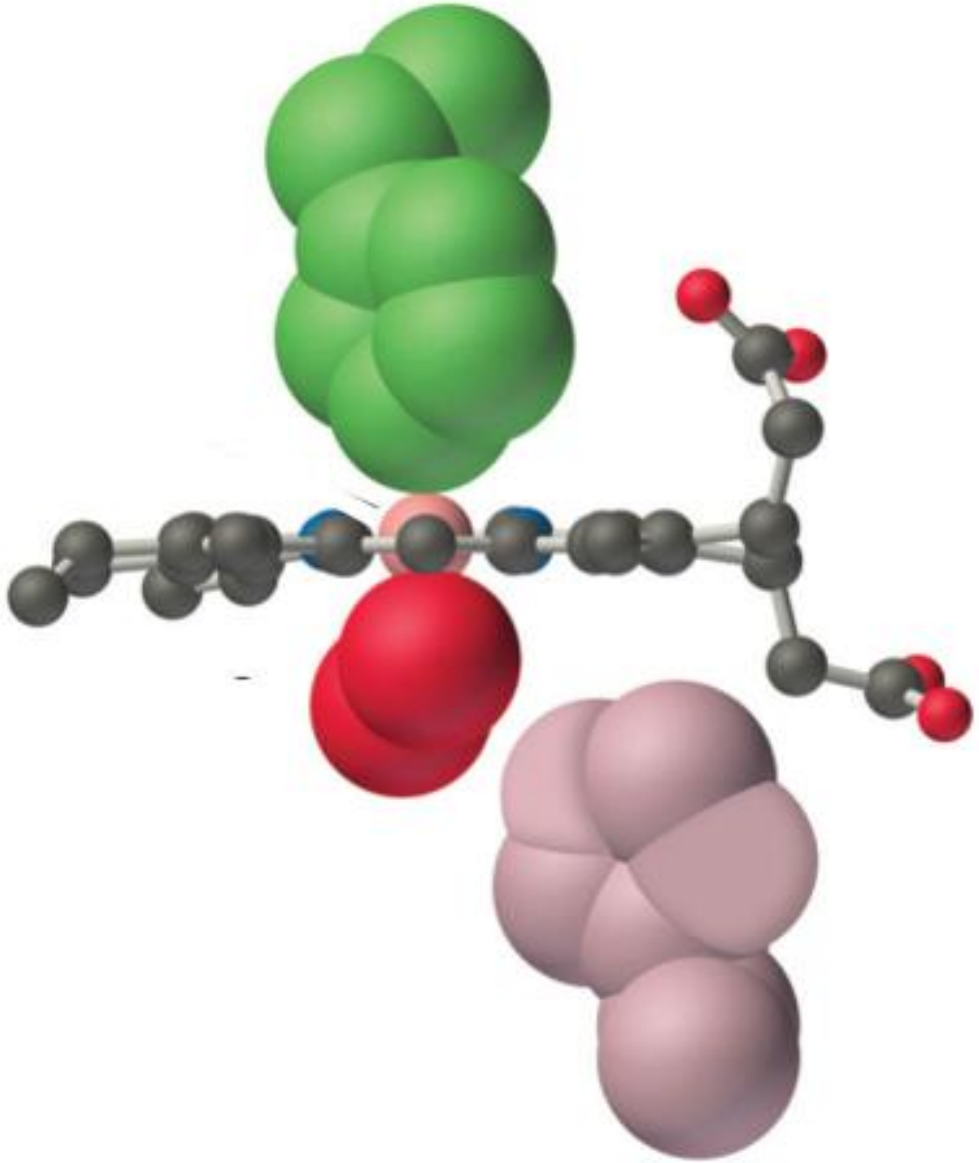
- A **standard drink** = 14 g ethanol
  - 12 oz of regular beer or cooler (5% alcohol)
  - 5 oz of table wine (12% alcohol)
  - 1.5 oz of hard liquor (40% alcohol, 80 proof)
  - The average person metabolizes about 1 standard drink per hour



Source: National Institute on Alcohol Abuse and Alcoholism. Bethesda, Md: NIAAA; 2004. NIH Publication No. 04-3769.

Mechanisms of Action

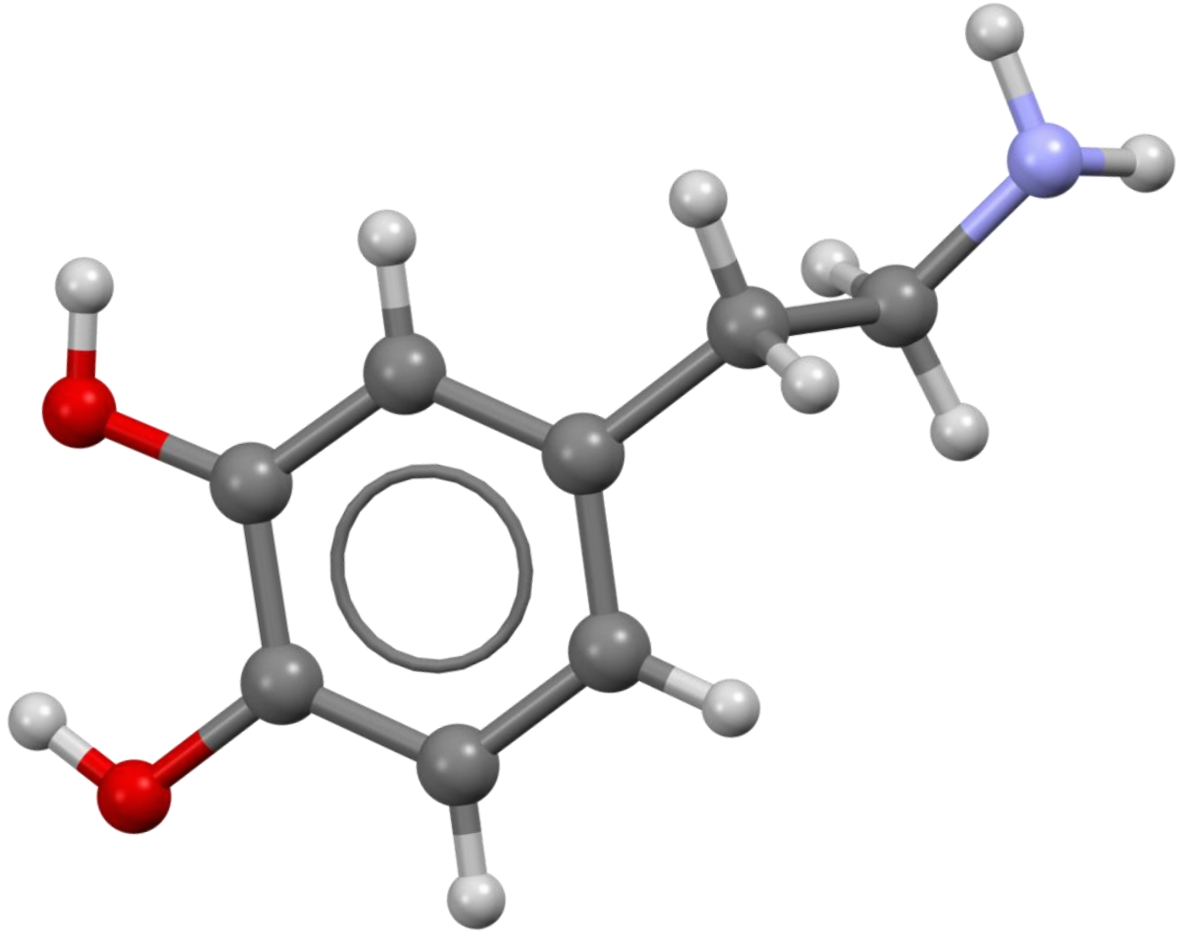
- Most drugs of abuse produce effects by binding to specific protein receptors on nerves.
- Alcohol is relatively indiscriminate and interacts with a variety of targets including proteins and lipids including voltage-gated and ligand-gated ion channels
- Generally, alcohol enhances GABA and glycine receptor function



Mechanisms of Action

Effects ion channels

- Inhibitory--$GABA_A$ and strychnine-sensitive glycine receptor
- Inhibitory—glutamate-activated channels (NMDA and non-NMDA N-methyl-D-aspartate)
- Excitatory-inhibits the inhibitory neurotransmitter adenosine
- Downregulates various cell receptors
  - **Increases midbrain (VTA) dopamine**
  - Increases certain opioids (*B*-endorphin)
  - Increases transmission through 5-HT3 receptors and cannabinoid system



Molecular properties of alcohol-sensitive ion channels

Neurotransmitter	Channel name	Major ions	Acute alcohol effect
GABA	$GABA_A$	Cl^-	enhance
Glycine	Glycine	Cl^-	enhance
Nicotinic Acetylcholine	nAchR	Na^+	enhance/inhibit
Serotonin	$5HT_3$	Na^+	enhance
ATP	$P2_X$	Na^+	inhibit
Glutamate	NMDA	Ca^{++}/ Na^+	inhibit
Glutamate	Non-NMDA	Ca^{++}/ Na^+	Inhibit(though relatively insensitive)
Voltage gated	BK_{Ca}	K^+	enhance
Voltage gated	L, N,P,Q,T	Ca^{++}	inhibit

Acute ingestion

Feeling of warmth due to increased cutaneous blood flow

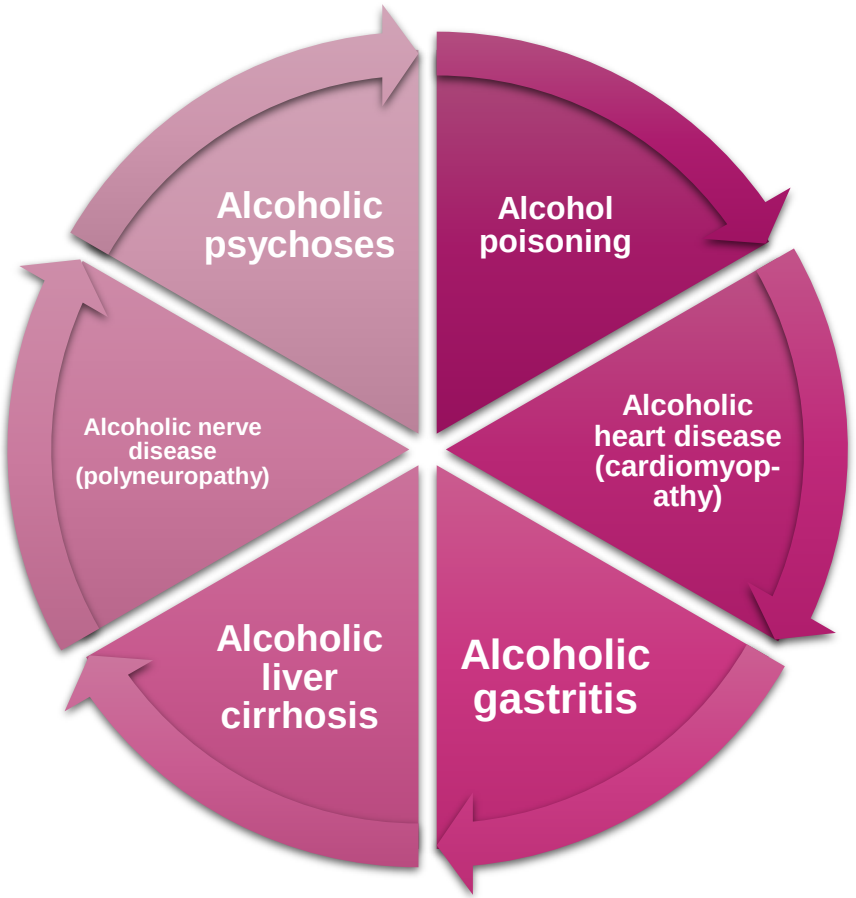
Initially increases gastric secretions; >20% concentration inhibits secretions

“Intoxication” can range from mild inhibition of normal responsible behavior (disinhibition) to a state of unconsciousness depending on dose and user’s drinking (and/or other drug use) history

It is a CNS sedative/hypnotic and anesthetic

Diseases Associated with Chronic Alcohol Use

Primary



Secondary

- Cancer (lip, mouth, pharynx, esophagus, larynx, liver, stomach)
- Diabetes
- Gastrointestinal disease
- Heart disease (hypertension, stroke)
- Liver disease
- Pancreatitis (acute, chronic)
- Pneumonia/influenza
- Tuberculosis

Sources: Schuckit MA. In: *Harrison's Principles of Internal Medicine*. New York: McGraw-Hill; 2001:2561-2566.

ADVERSE EFFECTS

Chronic Ingestion

CNS

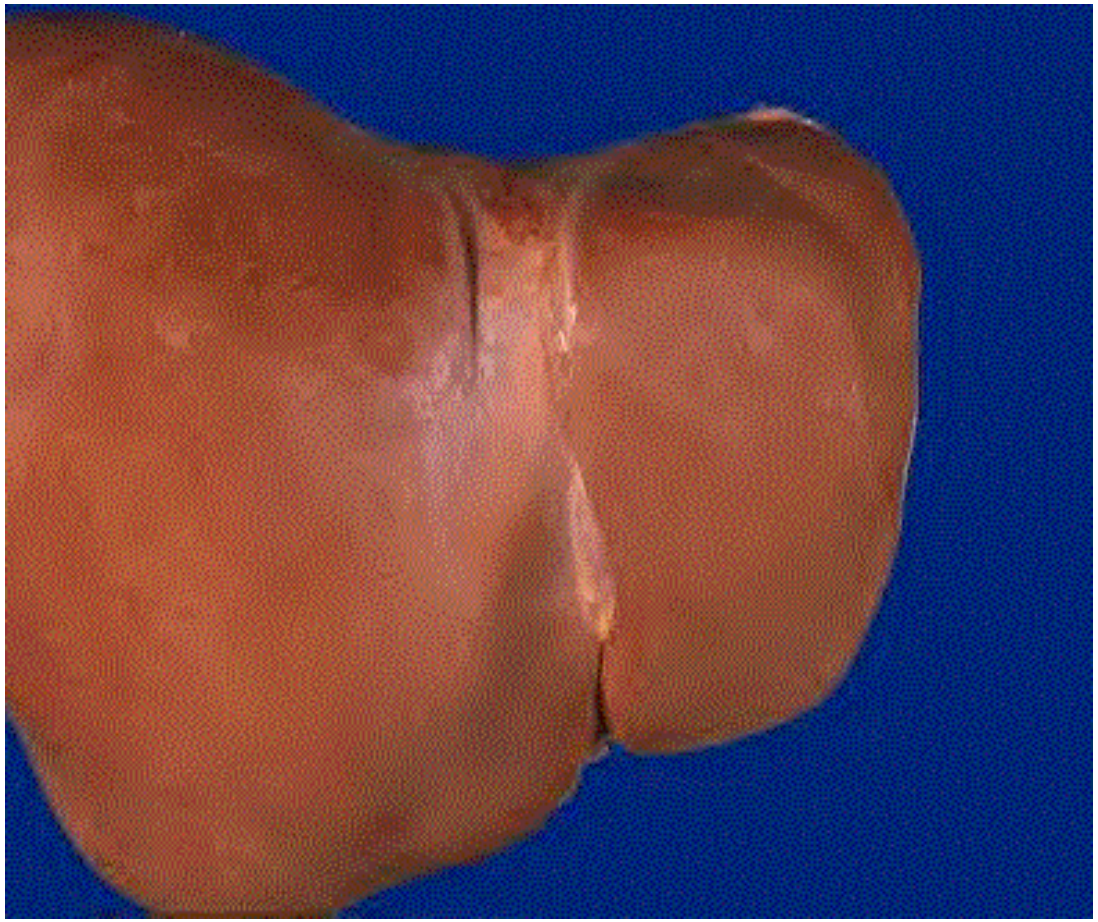
- depresses subcortex resulting in disinhibition;
- depresses cerebellum causing ataxia, slurred speech;
- depresses medulla causing respiratory death.
- Memory, judgement, learning impaired;
- Wernicke-Korsakoff's syndrome from thiamine deficiency.

GI

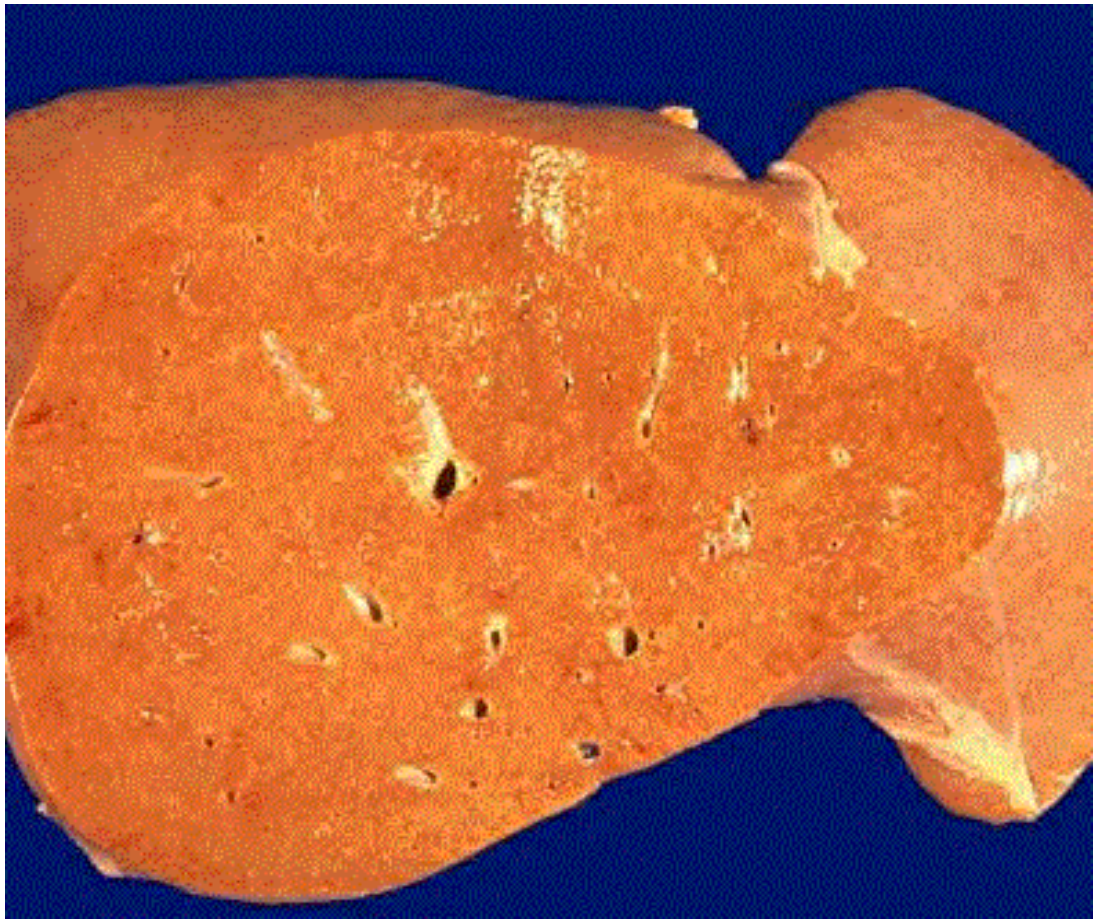
- protein and lipid deposition= fatty liver; inflammation=hepatitis; scarring=cirrhosis.
- Peptic ulcer disease,
- esophagitis,
- esophageal varices,
- pancreatitis,
- diarrhea,
- malnutrition and a
- variety of nutrient deficiencies

Liver Comparison

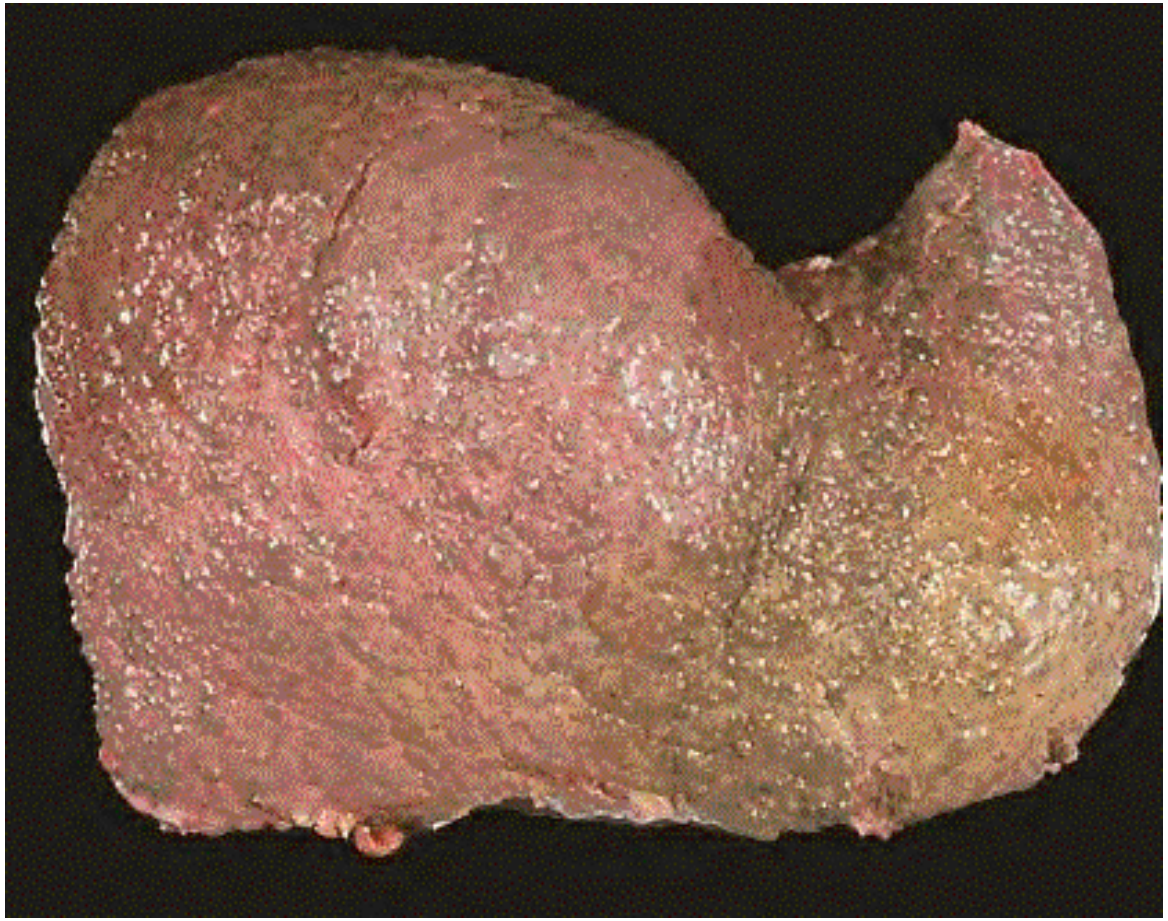
Normal liver

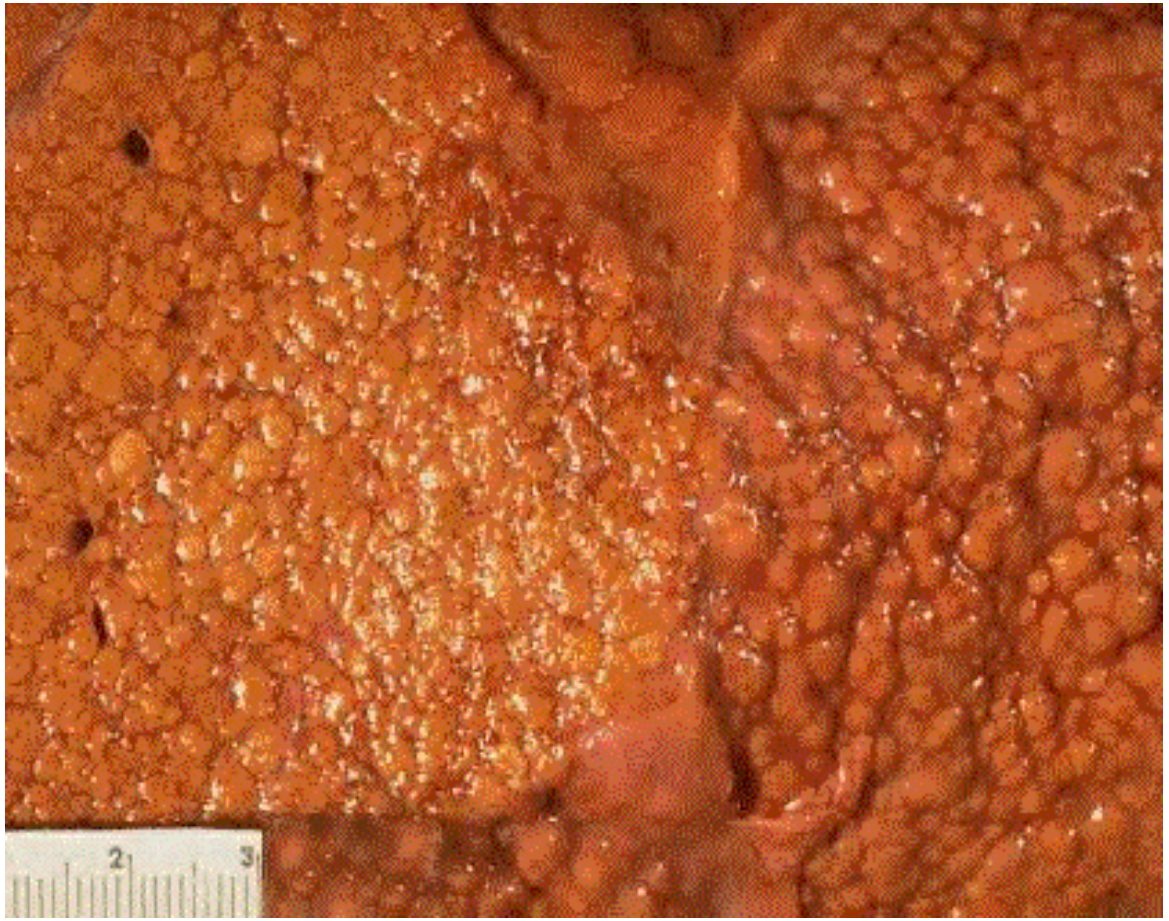


Fatty change

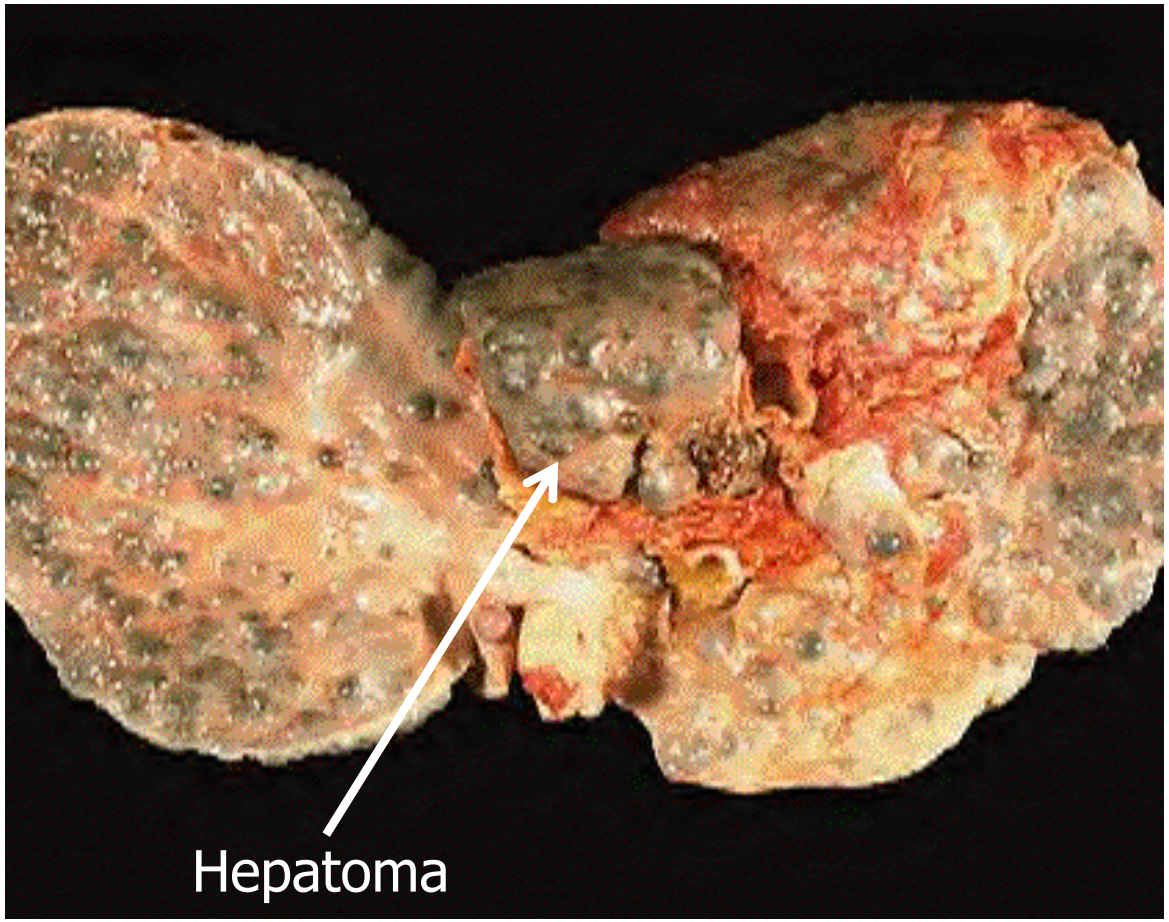


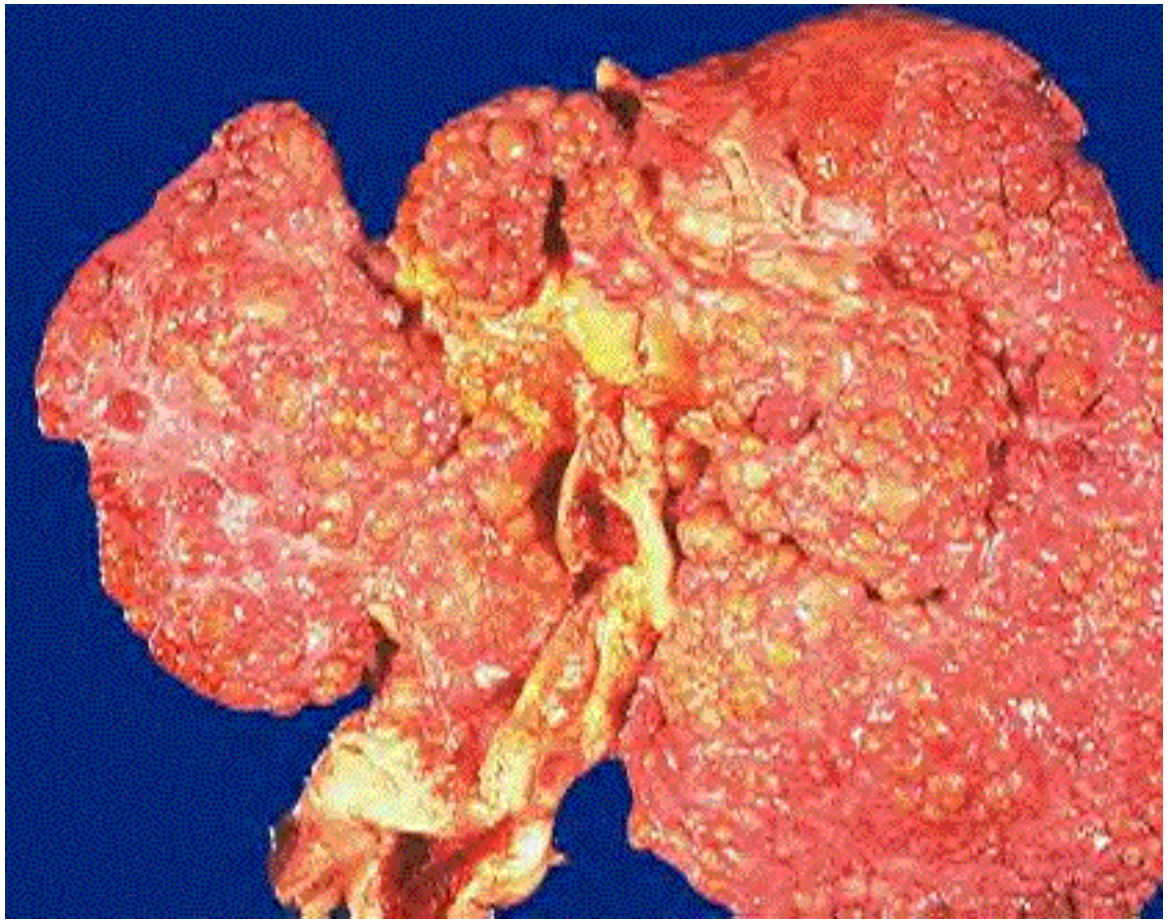
Micronodular cirrhosis





Macronodular Cirrhosis





ADVERSE EFFECTS

Chronic Ingestion

CV

- lower incidence of MI, stroke, HTN with low dose (1-2 drinks/day) but all increased with heavier use.
- CHF from alcoholic cardiomyopathy,
- “holiday heart” arrhythmias (Paroxysmal tachycardias)

Hematologic

- decreased RBC, WBC, platelets, coagulopathy, macrocytosis (increase MCV), immune suppression

ADDICTION LIABILITY AND REINFORCING PROPERTIES

- Uncontrolled use of alcohol despite adverse consequences, coupled with the existence of craving and alcohol-seeking behavior, characterizes the disease of alcoholism.

- Direct reinforcing properties, rapid development of high tolerance, and reduction of withdrawal symptoms with re-use promote more use.


Hey Kids!
Match the Cheap-Ass Beer with Its Slogan
alibi
What do I like to do on Friday nights?
Find Out
Match each beer with its slogan, then read across the redboxes to find out what this guy likes to do on Friday nights.
Prizes Include:
✓ Two $25 Wild Oats gift certificates
✓ A box of Wild Oats brand natural Belgian Chocolates
✓ FirmGrip Straight Peeler by Edge Resources
by Laura Marrich
Are you a bonafide gastronomical sleuth? Test your noodle with these food-based brainteasers and find out!
Answer the trivia questions on page 25, then match each down-market beer letter with its corresponding slogan on this page. Mail both sets of answers to "Food Quiz" at 2110 Central SE PMB 151, Albuquerque, N.M. 87106. The first person to correctly answer the trivia and match the beer will win a fabulous pile of prizes.
A B C D E F G H I J K L
"The Brew That Grew with the Great Northwest"
"Reach for the Silver Star"
"Unleash the Beast"
"The Beer Refreshing From the Land of Sky Blue Waters"
"A Beer to Call Your Own"
"The One Beer to Have When You're Having More Than One"
"Milwaukee's Finest Beer"
"Head for the Mountains"
"When You See the Three-Ring Sign, Ask the Man for ****"
"Always Smooth, Never Bitter"
"Hey, Mabel!"
"Gives You More of What You Drink Beer For"
"It's the Extra-Dry Treat"
"It Don't Get Any Better Than This"
"Pure Brewed in God's Country"
"The Champagne of Beers"
"Golden Quality Since 1851"
"Premium Pasteurized Beer"
"The Beer That Made Milwaukee Famous"
"From the Country of 1,100 Springs"
"All that Glitters is Not ****"
"When You Want to Chase a Beer with a Beer Bring on ****"
"Mountain Fresh Taste"
"It's the Water!"
M N O P Q R S T U V W X

“If the patient be in the prime of life and if from drinking he has trembling hands, it may be well to announce beforehand either delirium or convulsions.”

Hippocrates, c. 400 BCE

Alcohol Withdrawal

"It is preceded by tremors of the hands, restlessness, irregularity of thought, deficiency of memory, anxiety to be company, dreadful nocturnal dreams when the quantity of liquor throughout the day has been insufficient; much diminution of appetite, especially an aversion to animal food; violent vomiting in the morning and excessive perspiration from trivial causes. Confusion of thought arises to such height that objects are seen of the most hideous forms, and in positions that it is physically impossible they can be so situated; the patient generally sees flies or other insects; or pieces of money which he anxiously desires to possess..."

Sutton, 18th century

Alcohol Withdrawal

Withdrawal signs and symptoms may appear while patient is still drinking.

Withdrawal usually peaks 24 to 36 hours after the last drink.

Early signs include:

- anxiety
- agitation
- sweating
- headache
- nausea and vomiting
- insomnia
- tremor
- hypertension
- tachycardia
- auditory and tactile disturbances
- delirium

Alcohol Withdrawal-Pathophysiology

Alcohol enhances effect of GABA, the major inhibitory neurotransmitter and alcohol abstinence results in a relative GABA activity deficiency.

Alcohol inhibits the sensitivity of autonomic adrenergic systems with a resulting upregulation with chronic alcohol intake.

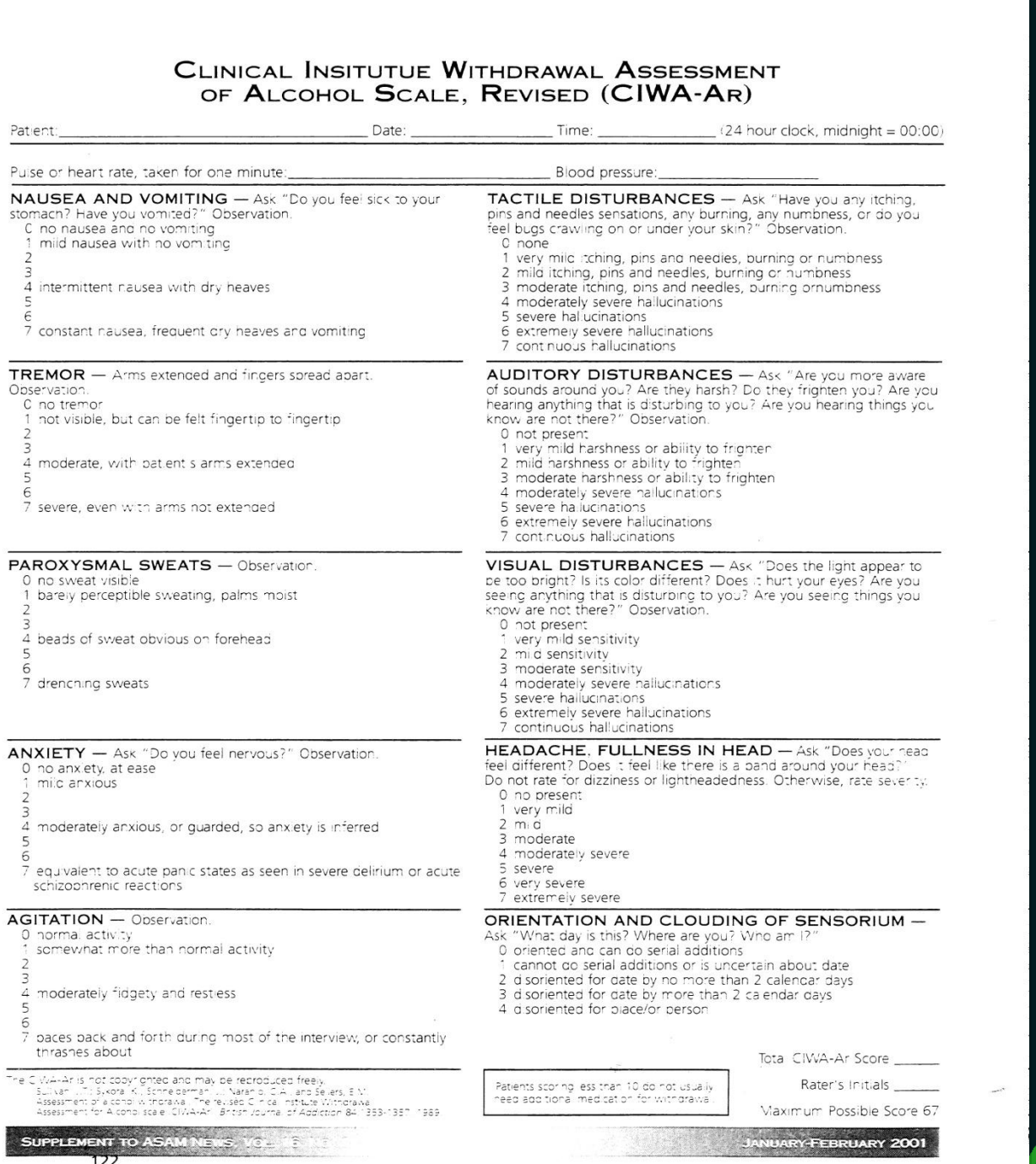
Abstinence leads to rebound overactivity and a hyper-adrenergic state.

Predictors of Withdrawal Severity

- prior history of severe withdrawal symptoms
- number of detoxifications
- quantity and duration of drinking
- high blood alcohol level without signs of intoxication
- withdrawal signs with high blood alcohol
- concurrent use of sedative/hypnotics
- significant coexisting medical problems
- CIWA-Ar >20

CIWA-Ar

- Clinical Institute Withdrawal Assessment for Alcohol scale, revised
- Sullivan, J.T., et alia, *British Journal of Addiction* 84:1353-1357, 1989.
- Not copyrighted, so can be reproduced and distributed freely
- only studied in alcohol treatment programs so efficacy outside such program is not clear



Clinical Institute Withdrawal Assessment of Alcohol Scale, Revised (CIWA-Ar)

Patient:_____ Date: _____ Time: _____ (24 hour clock, midnight = 00:00)

Pulse or heart rate, taken for one minute:_____ Blood pressure:_____

NAUSEA AND VOMITING — Ask "Do you feel sick to your stomach? Have you vomited?" Observation.
0 no nausea and no vomiting
1 mild nausea with no vomiting
2
3
4 intermittent nausea with dry heaves
5
6
7 constant nausea, frequent dry heaves and vomiting

TREMOR — Arms extended and fingers spread apart. Observation.
0 no tremor
1 not visible, but can be felt fingertip to fingertip
2
3
4 moderate, with patient's arms extended
5
6
7 severe, even with arms not extended

PAROXYSMAL SWEATS — Observation.
0 no sweat visible
1 barely perceptible sweating, palms moist
2
3
4 beads of sweat obvious on forehead
5
6
7 drenching sweats

ANXIETY — Ask "Do you feel nervous?" Observation.
0 no anxiety, at ease
1 mildly anxious
2
3
4 moderately anxious, or guarded, so anxiety is inferred
5
6
7 equivalent to acute panic states as seen in severe delirium or acute schizophrenic reactions

AGITATION — Observation.
0 normal activity
1 somewhat more than normal activity
2
3
4 moderately fidgety and restless
5
6
7 paces back and forth during most of the interview, or constantly thrashes about

TACTILE DISTURBANCES — Ask "Have you any itching, pins and needles sensations, any burning, any numbness, or do you feel bugs crawling on or under your skin?" Observation.
0 none
1 very mild itching, pins and needles, burning or numbness
2 mild itching, pins and needles, burning or numbness
3 moderate itching, pins and needles, burning or numbness
4 moderately severe hallucinations
5 severe hallucinations
6 extremely severe hallucinations
7 continuous hallucinations

AUDITORY DISTURBANCES — Ask "Are you more aware of sounds around you? Are they harsh? Do they frighten you? Are you hearing anything that is disturbing to you? Are you hearing things you know are not there?" Observation.
0 not present
1 very mild harshness or ability to frighten
2 mild harshness or ability to frighten
3 moderate harshness or ability to frighten
4 moderately severe hallucinations
5 severe hallucinations
6 extremely severe hallucinations
7 continuous hallucinations

VISUAL DISTURBANCES — Ask "Does the light appear to be too bright? Is its color different? Does it hurt your eyes? Are you seeing anything that is disturbing to you? Are you seeing things you know are not there?" Observation.
0 not present
1 very mild sensitivity
2 mild sensitivity
3 moderate sensitivity
4 moderately severe hallucinations
5 severe hallucinations
6 extremely severe hallucinations
7 continuous hallucinations

HEADACHE, FULLNESS IN HEAD — Ask "Does your head feel different? Does it feel like there is a band around your head?" Do not rate for dizziness or lightheadedness. Otherwise, rate severity.
0 not present
1 very mild
2 mild
3 moderate
4 moderately severe
5 severe
6 very severe
7 extremely severe

ORIENTATION AND CLOUDING OF SENSORIUM — Ask "What day is this? Where are you? Who am I?"
0 oriented and can do serial additions
1 cannot do serial additions or is uncertain about date
2 disoriented for date by no more than 2 calendar days
3 disoriented for date by more than 2 calendar days
4 disoriented for place/or person

Total CIWA-Ar Score _____
Rater's Initials _____
Maximum Possible Score 67

Patients scoring less than 10 do not usually need additional medication for withdrawal.

The CIWA-Ar is not copyrighted and may be reproduced freely.
Sullivan, J.T., Sykora, K., Schneiderman, J., Naranjo, C.A., and Sellers, E.M. Assessment of alcohol withdrawal: The revised Clinical Institute Withdrawal Assessment for Alcohol scale (CIWA-Ar). *British Journal of Addiction* 84:1353-1357, 1989.

CIWA-Ar

10 QUESTIONS SCORED 0 - 7

REQUIRES ABOUT 5 MINUTES TO ADMINISTER

PATIENTS SCORING MORE THAN 20 SHOULD BE ENCOURAGED TO BE ADMITTED TO A HOSPITAL

PATIENTS SCORING LESS THAN 10 USUALLY DO NOT NEED ADDITIONAL MEDICATION FOR WITHDRAWAL

CIWA-Ar

Do not interpret CIWA-Ar in a clinical vacuum!

- A score of 10 with BAC of 100mg% may presage severe withdrawal
- Elderly; medically complicated patients with CAD, HTN, DM, COPD may be unable to tolerate even mild hyper-adrenergic syndrome
- Other drugs may lower score without reducing the potential for seizures and/or delirium
  - beta blockers, alpha agonists, calcium channel blockers
  - surreptitious use of sedative/hypnotics or other drugs

Alcohol Withdrawal Hallucinosis

Visual

-lights too bright

-see animals like dog or rodent

-may progress to frank hallucinations

Auditory

- sounds too loud or startling
- unformed sounds like clicks or buzzes
- may progress to formed voices

Tactile

bugs or insects crawling on or under skin

Alcohol Withdrawal Hallucinosis

Milder Stages of Withdrawal:
Patient's sensorium is otherwise clear and the patient retains insight that the hallucinations are not real.

Severe Withdrawal: This insight is lost.

Alcohol Withdrawal Seizures

Occur within 8-24 hours after the last drink
Can occur with alcohol in bloodstream
Most are generalized tonic/clonic motor or “grand mal”
Single or burst of several over 1-6 hours
Increased risk with previous withdrawal seizure (kindling effect), chronic seizure disorder, concurrent benzodiazepine or other sedative/hypnotic withdrawal

- **anticonvulsants are <u>not</u> recommended for routine or prophylactic use**
- adequate benzodiazepines or barbiturates given for detox should suffice
- diagnostic evaluation should be considered for first or atypical seizures

Alcohol Withdrawal Delirium

Onset

- manifest by continually worsening withdrawal symptoms which can progress to a life-threatening delirium accompanied by an autonomic storm--hence delirium tremens (DT's)
- usually appears 72-96 hours after last drink
- most severe symptoms can last a few hours or up to a week; usually about 2-3 days
- confusion can last several weeks

Symptoms

- hyperadrenergic state
  - tachycardia, fever, tremor, sweating
- global confusion, disorientation to place and time
- hallucinations which may be extremely frightening to patient
- marked psychomotor activity which may require seclusion or restraints
- 1-5% mortality even with treatment

Alcohol Withdrawal Delirium

Higher Risk

- blood alcohol >300 at presentation
- previous DT's
- following withdrawal seizure
- older individuals
  - Especially those with concurrent medical problems
  - Patients hospitalized for other medical or surgical problems (~20% of adults admitted to hospitals for any reason have alcohol use disorders)
- **Treatment requires intensive hospital intervention and monitoring**

Alcohol Withdrawal- Pharmacologic Management

Fixed schedule dosing

- Chlordiazepoxide 50 mg q6h x 8 doses, then 25 mg q6h x 4 doses.
  - Hold any dose for excessive sedation.
- Can use other Bzd's at equivalent doses:

  diazepam 10 mg ⇨ 5 mg

  lorazepam 2 mg ⇨ 1 mg

  oxazepam 30 mg ⇨ 15 mg

  clonazepam 1-2mg ⇨ **0.5-1 mg**
- Avoid barbiturates and alprazolam (Xanax)

Alcohol Withdrawal- Pharmacologic Management

Symptom-triggered dosing

- requires the use of a structured assessment scale and medication is given based on the score of the scale
- reduced amount of medication given
- reduced duration of treatment

- *most commonly used scale for alcohol withdrawal is the CIWA-Ar*

Alcohol Withdrawal- Pharmacologic Management

Adjunctive medications

Pharmacologic

- anti-hypertensives
  - propranolol (Inderal), atenolol (Tenormin)
  - clonidine (Catapres), lofexidine
- anti-seizure
  - carbamazepine (Tegretol), valproate (Depakote), gabapentin
- anti-psychotics
  - haloperidol (Haldol), olanzapine (Zyprexa), risperidone (Risperdal)
- ***Some may mask withdrawal symptoms and may not reduce delirium and/or seizures. Antipsychotics can lower seizure threshold***

Natural

- thiamine 100 mg daily
- multivitamin with folate and no iron
- magnesium
- amino acid supplementation
- alpha-lipoic acid
- herbs
  - milk thistle/silymarin
  - kudzu extract

Alcohol Withdrawal- Pharmacologic Management

REMEMBER

Alcohol withdrawal can be managed as an outpatient with minimal prescriptive medication supplementation 90% of the time ***if you are confident with the completeness and accuracy of your initial comprehensive evaluation!***

PHARMACOLOGIC THERAPIES

To Assist in Recovery

Disulfiram (Antabuse)

Binds irreversibly to and inhibits ALDH causing accumulation of acetaldehyde.

- Can reduce clearance of Librium or Valium, imipramine or desipramine, phenytoin and warfarin.
- Can inhibit dopamine beta hydroxylase **increasing** dopamine levels.

Side effects:

- exacerbation or uncovering of schizophrenia
- drowsiness
- headache
- hypertension
- burning paresthesias
- peripheral neuropathy
- optic neuritis
- hepatitis
- acute liver failure

PHARMACOLOGIC THERAPIES

Calcium Carbimide (Temposil)

short acting, reversible inhibitor of ALDH. Seems to be safer than Disulfiram. Available in Europe, Canada. Developed by Dr Gordon Bell

Beta-blockers

atenolol

Serotonergic agents

SSRI's

Benzodiazepines/Anxiolytics

may reduce anxiety and improve retention in treatment. Problematic risk/benefit ratio with Bzd's!

Naltrexone (ReVia, Trexan)

po or depot IM

Can be started before discharge on inpatients

Phenothiazines/dopaminergic blockers

Similar to Bzd's.

Lithium carbonate

useful if they have co-morbid bipolar disorder

Hallucinogens

LSD, MDMA, Ibogaine, psilocybin/psilocin…

Topamax

topiramide

Calcium acetylhomotaurinate (Acamprosate)

amino acid derivative which affects both inhibitory gamma-aminobutyric acid (GABA) and excitatory glutamate neurotransmission. Possibly decreases craving (?)

Glacier Bay National Park 2006

Thank you for attending!

Please reach out with any questions you may have.

Minnesotaasam@acentra.com

https://mhcp.acentra.com/