ASAM REVIEW COURSE 2023

Alcohol Use Disorder: Neurobiology, Diagnosis and Treatment

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REVIEW COURSE 2023

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Outline

1. Historical View
2. Neurobiology
3. Epidemiology
4. SBIRT and Clinical Screening Test
5. Diagnosis
6. Biomarkers
7. Phases of Alcohol Treatment and Related Syndromes
8. CIWA-Ar and Management
9. Relapse Prevention Pharmacotherpy and Psychotherapy
10. New Directions
11. Conclusion

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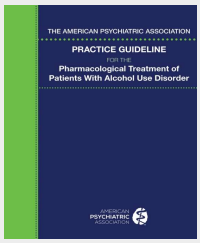
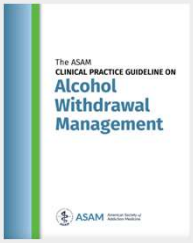
APA Practice Guideline for the Pharmacological Treatment of Patients With Alcohol Use Disorder

December 2017



ASAM Clinical Practice Guideline on Alcohol Withdrawal Management

January 2020



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Historical View: Alcohol Use Disorder an Ancient Problem or a Disease?

After the flood, Noah plants a vineyard, makes wine and gets drunk. (Genesis 9:21)

"Who hath woe? Who hath sorrow? Who is always fighting? Who is always complaining? Who hath wounds without cause? Who has bloodshot eyes?

They who tarry long at the wine; when it sparkles in the cup. Don't let the smooth taste deceive you. For in the end it bites like a poisonous serpent. And you will say, 'They hit me, but I didn't feel it.'

Your eyes will see strange visions and you will say strange thoughts. Yet when you awaken, you seek it yet again."
(Proverbs 23:29 (~1,000 BC)

Pliny the Elder: Gaius Plinius Secundus Naturalis Historia: "drunkeness brings pallor and sagging cheeks, sore eyes, and trembling hands that spill a full cup, of which the immediate punishment is a haunted sleep and unrestful nights..."

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Case: RR

Mr. RR is a 58 –year-old, Latino, married, male owner of a music theater in Los Angeles. He is being referred for evaluation to assess his drinking and depression after his older brother, who in the past had problems with alcohol, recommended him.

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Case: RR

He presents for his evaluation thinking alcohol helps him to manage:

- Depression
- Insomnia
- Irritability and anxiety

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Case: RR

SA history: He reports that he grew up drinking. His first drink was at age four when he tasted the left-over alcohol from a party in his family home. He describes falling in love with the taste of wine and waited every weekend for his family to throw another party.

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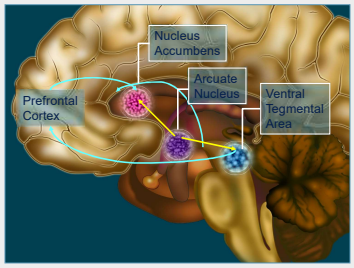
Alcohol Use Disorder a Disease?



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Neurotransmitter Systems

GABA	→	CNS Inhibition
Glutamate	→	CNS Excitation
Opioid	→	Euphoria
Dopamine	→	Addiction
Serotonin	→	Impulsivity
Cannabinoid	→	Pleasant Feeling

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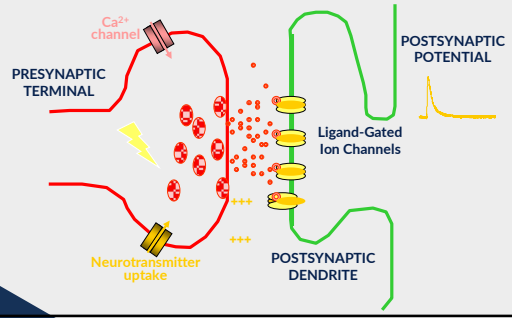
Steps in Synaptic Transmission



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Case: RR

Substance abuse h/x and symptoms

He then started to drink at age 12 years old on weekends and continued daily for the past 30 years. While he had difficulties quantifying the amount he consumes, he states that he rarely has "too much," although he admits occasionally missing work due to hangovers and driving while intoxicated (luckily, no accidents, no DUI).

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Case: RR

Substance abuse h/x and symptoms

His last drink was the previous night. He explained he often has diarrhea and shakes in the morning, which he attributes to "anxiety" because these symptoms are alleviated with 1 or 2 alprazolam that has been prescribed by his PCP for the past decade.

No other drugs or substance use history.

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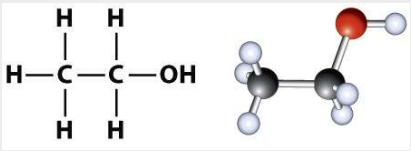
Alcohol (Ethanol C2 O1 H6)



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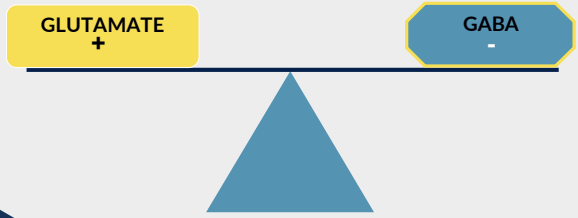
Acute Alcohol Intake



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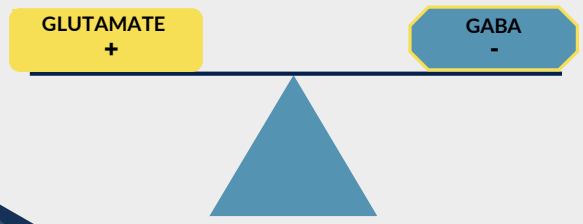
Chronic Alcohol Intake



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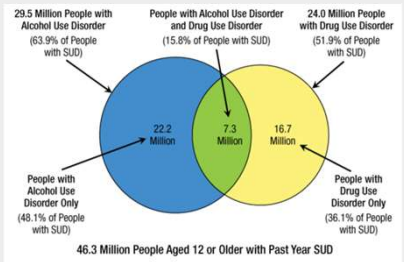
Alcohol Use Disorder and Drug Use Disorder in the Past Year: Among People Aged 12 or Older with a Past Year Substance Use Disorder (SUD); 2021



Note: Drug Use Disorder includes data from all past year users of marijuana, cocaine, heroin, hallucinogens, inhalants, methamphetamine, and prescription psychotherapeutic drugs (i.e., pain relievers, tranquilizers, stimulants, or sedatives)

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Epidemiology
Scope of Alcohol-Related Problems

- ~140,000 people die (380 per day) annually from alcohol-related causes in the U.S from 2015-2019
- Nearly 29.5 million people ages 12 and older had AUD in 2021
- 894,000 adolescents ages 12 to 17 with AUD in 2021
- 4th leading preventable cause of death in U.S. is AUD

Sources: CDC 2022 ; SAMHSA Prevalence – NSDUH (2021 and 2015)

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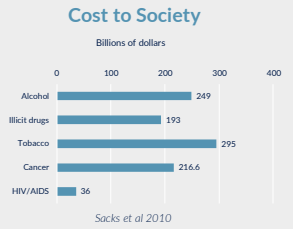
Cost and Scope of Alcohol-Related Problems



Sacks et al 2010

- ~ 50% of U.S. liver disease deaths attributable to alcohol misuse (2021)
- Increase 50% in emergency department visits and hospitalizations related to alcohol between 2006-2014
- Among people who die by suicide, AUD is the second most common mental disorder and involved in roughly 1 in 4 deaths by suicide

Sources: Prevalence – NSDUH (2021, 2019), NIH 2023

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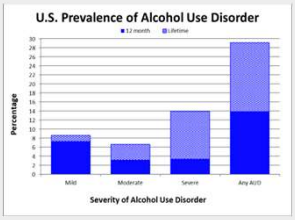
Epidemiology/Prevalence

Prevalence:

- Worldwide (Slade et al., 2016)
  - Lifetime 20%
  - 12 month 8.5%
  - In 2012 about 3.3 millions deaths, or 5.9 % of a global deaths, were attributable to alcohol consumption
- U.S. (Grant et al. 2015, 2017)
  - Lifetime 29%, with severe alcohol use disorder (AUD) in about half
  - 12-month 13.9 %
  - 12-month rates of AUD increased by ~50% between 2001-2002 and 2012-2013



Based on data from Grant et al. Epidemiology of DSM-5 alcohol use disorder: results from the National Epidemiologic Survey on Alcohol and Related Conditions III. JAMA Psychiatry. 2015 Aug;72(8):757-66. (Information shared by APA)

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Epidemiology/Demographics

AUD affects individuals of all demographic groups

- Onset: 18-29 years
- Ethnicity (12-month prevalence):
  - American Indian/Alaska Native 19.2%
  - African American 14.4%
  - White 14%
  - Hispanic 13.6%
  - Asian-American/Pacific Islander 10.6%
- Gender (12-month prevalence):
  - Men 17.6%
  - Women 10.4%

Grant et al. 2015

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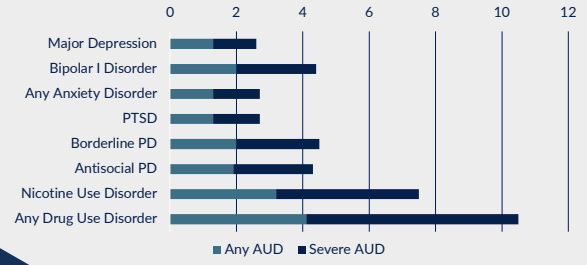
Adjusted Odds Ratios of Lifetime AUD and Other Conditions



Based on data from Grant et al. JAMA Psychiatry. Aug;72(8): 757-66, 2015 (information shared by APA)

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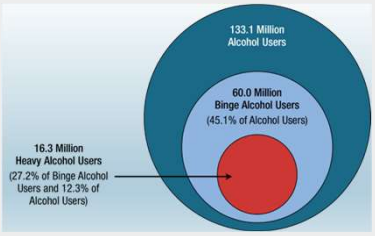
Past Month Alcohol Use, Binge Alcohol Use, and Heavy Alcohol Use: Among People Aged 12 or Older; 2021



Note: Binge Alcohol Use is defined as drinking five or more drinks (for males) or four or more drinks (for females) on the same occasion on at least 1 day in the past 30 days. Heavy Alcohol Use is defined as binge drinking on the same occasion on 5 or more days in the past 30 days; all heavy alcohol users are also binge alcohol users.

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Prevalence of Alcohol Use Disorder:

Current, Binge, and Heavy Alcohol use among people 12 and 18 or older in the lifetime and past month; 2021

- 84 %of people ages 18 and older reported that they drank alcohol at some point in their lifetime
- 21.5% percent of people ages 12 and older reported that they engaged in binge drinking in the past month
- 5.8 % % people ages 12 and older reported that they engaged in heavy alcohol use in the past month

NIAAA National Institute on Alcohol Abuse and Alcoholism; SAMHSA NSDUH 2021

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How Much is "too much"?

Heavy Drinking

- WOMEN:
  4 or more standard drinks in a sitting.
  (8 or more per week.)
- MEN:
  5 or more standard drinks in a sitting.
  (15 or more per week.)

Binge Drinking

- A pattern of drinking that brings blood alcohol concentration (BAC) levels to 0.08g/dl
- WOMEN:
  4 or more drinks on same occasion in about 2 hours
- MEN:
  5 or more drinks in same occasion in about 2 hours

Emerging Trend- High Intensity Drinking

Consuming ETOH at levels that are two or more times the gender-specific binge drinking thresholds

10 or more standard drinks (or alcoholic drink equivalents) for males and 8 or more for females

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COVID and Alcohol Use Disorder

- Data from a national survey of U.S. adults on their drinking habits found that excessive drinking (such as binge drinking) increased by 21% during the COVID-19 pandemic.
- More than a dozen studies have found that 20% to 40% of individuals surveyed reported consuming more alcohol than usual during the pandemic, based on National Institute on Alcohol Abuse and Alcoholism (NIAAA) information

NIAAA National Institute on Alcohol Abuse and Alcoholism 2021

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Adults are Drinking More Alcohol than a Decade Ago

A binge is defined as four drinks in two hrs for a woman and five drinks in two hrs for a man.

2002

- 65.4% Past Year Drinking
- 21.5 % Monthly Binge Drinking

2013

- 72.7% Past Year Drinking
- 25.8 % Monthly Binge Drinking

National Epidemiologic Survey on Alcohol and Related Conditions (NESARC), NESARC-III

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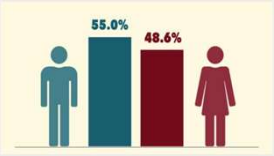
Alcohol use is increasing more in women than men in USA

Monthly Alcohol Use

Percentage of U.S men and women who reported drinking alcohol in the past month



Over the last century, gaps between males and females have narrowed for prevalence of drinking, total amount consumed, frequency, binge drinking, early onset drinking, having alcohol use disorder, drunk driving and self reported consequences

In the last decade differences narrowed further. Rates of alcohol use disorder (AUD) have increased in women by 84% over the past ten years relative to a 35% increase in men (Grant et al., 2017),

Women are more likely to experience blackouts, liver inflammation, brain atrophy cognitive deficits and some cancers. (Slade T et al. BMJ 2016)

2021 National Survey on Drug Use and Health

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Population-based epidemiological surveys show harmful drinking levels on the rise

Age is a known factor in heavy drinking.

Year	Respondents	Past Year	Lifetime	Source
1995-2002	adults	6.8% - 8.5%	13% - 23%	NESARC I, II 1997, 2004
2011	adults	13.9%	29.1	NESARC III 2015
2011	18-19 years	26.7%	37%	NESARC III 2015

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DSM-5 : Criteria for Alcohol Use Disorders

1. Use In Larger Amounts / Longer Periods Than Intended
2. Unsuccessful Efforts To Cut Down
3. Excessive Time Spent Taking Drug
4. Failure To Fulfill Major Obligations
5. Continued Use Despite Knowledge Of Problems
6. Important Activities Given Up
7. Recurrent Use In Physically Hazardous Situations
8. Continued Use Despite Social Or Interpersonal Problems
9. Tolerance
10. Withdrawal
11. Craving

Severity:
0 To 1 Criteria: No Diagnosis
2 To 3 Criteria: Mild
4 To 5 Criteria: Moderate
6 Or More Criteria: Severe

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Underdiagnoses and Unmet Treatment Needs

- Only 1 in 6 US adults report ever having asked by a clinician about their drinking behavior
- Despite high prevalence, societal cost, and available treatments, AUD remains undertreated
- <1 in 10 with a 12-month AUD diagnosis receive any treatment:
  - Self-help groups
  - Psychotherapy
  - Pharmacological treatments
- Treatment received by patients varies based on geography, insurance coverage, and formulary restrictions

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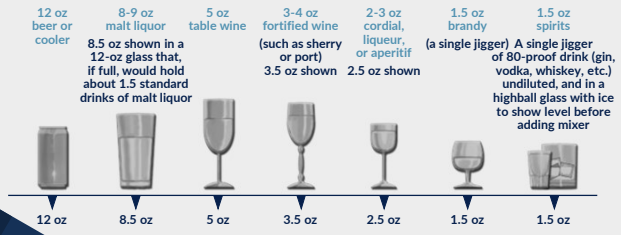
What is a standard drink?

- 1 Standard Drink = 14 gr. (0.6 oz.) of pure alcohol.
- The average person metabolizes about 1 Standard Drink per hour.



Adapted from www.niaaa.nih.gov.

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Intoxication Features

1 drink → BAC = ~15 mg% (0.015 g/dl)

BAC mg %	Clinical Manifestation
0-100 mg/dl	Well-Being
100-200 mg/dl	Incoordination
200-300 mg/dl	Ataxia
300-400 mg/dl	Stage 1 Anesthesia, amnesia, hypothermia
400-600 mg/dl	Coma
600-800 mg/dl	Death

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The Rules of Twenties

Going Up

- MEN: Each drink adds 20 mg/dL to one's BAL.
- WOMEN: Each drink adds 40 mg/dL to one's BAL.

Coming Down

- We metabolize 20 mg/dL every 60-90 minutes (zero order kinetics).

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Women and Pregnancy

- There are three general reasons that females show higher BACs (and greater intoxication) than males if they drink the same amount of alcohol.
- Body composition: In females a greater percentage of body mass is fat compared to males
  - Result – The concentration of alcohol is increased in the female bloodstream compared to the male body
- Stomach alcohol dehydrogenase (ADH): Females have very little of this enzyme compared to males
  - Result – Females do not metabolize alcohol before it gets out of the stomach. Therefore, the blood alcohol concentration (BAC) is higher for females versus males
- Liver ADH: Females have a less active form of this enzyme than males.
  - Result – Females do not metabolize alcohol as efficiently as males, thereby increasing the BA

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Women and Pregnancy

Fetal Alcohol Spectrum disorders (FASD): Growth retardation, Facial malformations, Small head, Greatly reduce intelligence.

- FASD is the most common known preventable cause of mental impairment.
- The prevalence of FASD : 50 per 1,000 (May et al., 2009 and CDC 2016)
- 40,000 infants per year in US

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Case: RR

Past Medical h/x: HTN for 10 years, GERD and H/x of pancreatitis.

Medications:

- Lisinopril 40 mg qam,
- Omeprazole 20 mg daily
- Zolpidem XR 6.25 mg qhs prn for insomnia
- Alprazolam 1-2 mg tid a day for anxiety.

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Case: RR

Vital Signs: BP:150/95
Pulse: 90x'

CBC normal with the exception of Increased MCV equal 102 (80-96)
Electrolytes and renal function: normal
Hepatic function:

- GGT 141 (10-42),
- AST 60 (15-40)
- ALT 40 (10-40)
- AST/ALT ratio 1.5
- CDT score exceeded the cutoff and so you performed a diagnostic evaluation

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Preventing and Treating AUD

There are evidence-based interventions for preventing and treating AUD:

- Screening, Brief Intervention, and Referral to Treatment (SBIRT)
- Professionally-led behavioral interventions
- FDA-approved medications
- Mutual support groups, such as Alcoholics Anonymous

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SBIRT

- Screening quickly assesses the severity of substance use and identifies the appropriate level of treatment.
- Brief intervention focuses on increasing insight and awareness regarding substance use and motivation toward behavioral change.
- Referral to Treatment provides those identified as needing more extensive treatment with access to specialty care.

www.niaaa.nih.gov/guide
http://www.sbirtcolorado.org/healthcare_videosandwebcasts.php

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Screening Tools

Alcohol Screening is an Effective Prevention Strategy

The CAGE Questionnaire

- Cut Down
- Annoyed
- Guilty
- Eye-Opener

2 or more positive responses are strongly associated with alcohol dependence.

National Institute on Alcohol Abuse and Alcoholism (NIAAA): "Helping Patients Who Drink Too Much"

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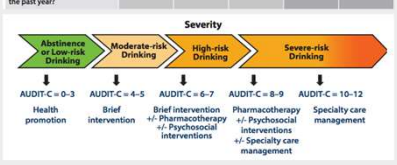
AUDIT-C Questionnaire

Alcohol Use Disorder Identification Test

Question	0 Points	1 Point	2 Points	3 Points	4 Points
How often did you have a drink containing alcohol in the past year?	Never	Monthly or less	2–4 times per month	2–3 times per week	4 or more times per week
On days in the past year when you drank alcohol how many drinks did you typically drink?	1–2	3–4	5–6	7–9	10 or more
How often do you have 6 or more drinks on an occasion in the past year?	Never	Less than monthly	Monthly	Weekly	Daily or almost daily



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The Role of Biomarkers in The Treatment of ETOH

- Provide objective outcome measures in alcohol research or evaluating an alcohol treatment program.
- Screen for individuals unable/unwilling to accurately report drinking behavior (e.g., fear, embarrassment, or adverse consequences).
- Evidence of abstinence in individuals prohibited from drinking.
- Enhance patient motivation to stop/reduce drinking.
- Diagnosis tool by assessing contribution of alcohol to the disease.
- Identify relapse early.
- Fear of detection by biomarkers may dissuade drinking.

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Types of ETOH Biomarkers

Indirect Tests
- Manifestations of organ damage often due to drinking
  - gamma glutamyltransferase (GGT)
  - aspartate amino transferase (AST, SGOT)
  - alanine amino transferase (ALT, SGPT)
  - macrocytic volume (MCV)
- Reflections of alcohol's effects on other metabolic processes -
  - carbohydrate-deficient transferrin (CDT) - Only FDA Approved alcohol biomarker

Direct Tests
- Reflections of alcohol use
  - ethyl glucuronide (EtG) and ethyl Sulfate (EtS)
  - Phosphatidylethanol (PEth)

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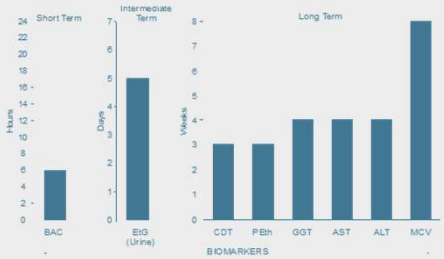
Window of Assessment for Various Alcohol Biomarkers



SAMHSA (Substance Abuse and Mental Health Services Administration) The Role of Biomarkers in the treatment of alcohol use disorders, 2012 Revision

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Characteristics of Assessment for Various Alcohol Biomarkers

Marker	Time to Return to Normal with Abstinence	Level of Drinking	Comments	Blood test normal range
GGT	2-4 weeks of abstinence	~ 5 drinks (>60g/day) for several weeks	Many sources of false positives—liver disease, diabetes, smoking, obesity, age, anticonvulsants, etc.	W: 0-45 U/L M: 0-53 U/L
SGOT/AST	2-4 weeks of abstinence	Unknown but heavy	Many sources of false positives (see GGT) in addition to excessive coffee consumption	10 - 34 U/L
SGPT/ALT	2-4 weeks of abstinence	Unknown but heavy	Many sources of false positives (see GGT) Less sensitive than AST	8-37 U/L
MCV	Up to several months	Unknown but heavy	Slow return to normal limits even with abstinence renders it a poor independent indicator of relapse. More specific than GGT. Unlike other markers, no strong gender effect	80-100fL
CDT	2-4 weeks	~ 5 drinks(>60g/day) for 2 weeks	Few sources of false positives. Good marker of relapse	<60 mg/L

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Diagnostic Sensitivity and Specificity of Biomarkers

	Sensitivity (%)	Specificity (%)
CDT	69	92
CDT/transferrin	65	93
GGT	73	75
AST	50	82
ALT	35	86
MCV	52	85

Bell, et al. Alcoholism: Clinical and Experimental Research 1994

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Case: RR

His last drink was the previous night. He explained he often has insomnia, diarrhea, palpitations, and shakes in the morning, which he attributes to "anxiety" because these symptoms are alleviated with 1 or 2 alprazolam that has been prescribed by his PCP for the past decade.

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Phases of Alcoholism Treatment

Detoxification
- Primary goal is to achieve an alcohol-free state
- Wide spectrum of severity
- Drug-specific syndromes: opiates, cocaine, alcohol, benzodiazepines

Relapse Prevention
- Primary goal is to maintain an alcohol-free state
- Chronic Treatment

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Introduction Alcohol Withdrawal

Epidemiology

Neurobiology
- Neurotoxicity
- Kindling

Management of Alcohol Withdrawal
- Benzodiazepines
- Anticonvulsants

Real World Implications
- Outpatient vs. Inpatient
- Evaluation and Management

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Epidemiology of Alcohol Withdrawal

- Not well studied
- Significant symptoms occur in 13% to 71% of individuals presenting for detoxification
- Up to 10% of individuals undergoing alcohol withdrawal require inpatient medical treatment
- Estimated mortality up to 2%

Saitz R, Mayo-Smith MF, Roberts MS, Redmond HA, Bernard, DR, Calkins DR. JAMA. 1994;272:519-523.

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Alcohol Withdrawal and Kindling

- Repeated episodes of alcohol withdrawal likely to worsen
- Exacerbation of symptoms may be due to a kindling process
- Positive relationship of alcohol withdrawal seizures to repeated detoxification

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Managing Alcohol Withdrawal

Principles of treatment

- Alleviate symptoms
- Prevent progression of symptoms
- Treat underlying comorbidities

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Alcohol Withdrawal Treatment

- Substitute cross-dependent drug (benzodiazepine)
- Gradually withdraw substitute drug
- Supplement vitamins and minerals
  - Thiamine
  - Folic acid
  - Multivitamin
- An array of acid–base disorders and electrolyte disorders can occur in patients with chronic alcohol-use disorder, irrespective of their social circumstances.
- Supportive treatment
  - Decrease stimulation, increase fluid and caloric intake

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Alcohol Withdrawal Treatment

Thiamine Deficiency

Thiamine
- Important cofactor for several enzymatic reactions
- Cerebral glucose utilization
- Glutamate elimination

Wernicke's Encephalopathy
- Partial to complete paralysis of extra ocular muscles
- Nystagmus
- Ataxia
- Mental disturbances
- Mortality: 10-20% if untreated
- Treatment: Thiamine replacement PRIOR dextrose administration

Korsakoff's Psychosis
- Antegrade amnesia
- Confabulations

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States of AWS

1. Autonomic Hyperactivity
2. Hallucinations
3. Neuronal excitation
4. Delirium Tremens

There is not necessarily a linear progression.

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States of AWS

Autonomic Hyperactivity
- Clear Sensorium
- Tremulous
- Diaphoresis
- Anxiety
- Nausea/Vomiting
- Increase cathecolamines in urine, serum and CSF
- Start 6 hrs after last drink Peak 24-48 hrs

Hallucinations
- Most common= VISUAL

Neuronal excitation
- Seizures (Generalized Tonic – Clonic)
- Up to 10%
- Most common in first 24 - 48 hours after last drink

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States of AWS

Delirium Tremens (DTs)

- Most often occur within 72 hours after the last drink
- Delirium with Tremor
- Autonomic hyperactivity
- Hallucinations
- Electrolyte abnormalities
- Dehydration
- Hemodynamic instability
- Mortality up to 15%
- Cardiovascular/respiratory collapse

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CIWA-Ar

Clinical Institute Withdrawal Assessment of Alcohol, Revised

- It requires under two minutes to administer
- It requires no medical knowledge
- It provides you with a quantitative score that predicts the severity of withdrawal from alcohol

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Assessment of Alcohol Withdrawal CIWA-Ar

Symptoms	Range of Scores
Nausea and Vomiting	0 (no nausea, no vomiting) -7 (constant nausea and/or vomiting)
Tremor	0 (no tremor) - 7 (severe tremors, even with arms not extended)
Paroxysmal sweats	0 (no sweat visible) - 7 (drenching sweats)
Anxiety	0 (no anxiety, at ease) - 7 (acute panic states)
Agitation	0 (normal activity) - 7 (constantly trashes about and pacing)
Tactile disturbances	0 (none) - 7 (continuous hallucinations)
Auditory disturbances	0 (not present) - 7 (continuous hallucinations)
Visual disturbances	0 (not present) - 7 (continuous hallucinations)
Headache	0 (not present) - 7 (extremely severe)
Orientation/clouding of sensorium	0 (orientated, can do serial additions) - 4 (Disorientated for place and/or person)

60

CIWA-Ar Determining Need of Pharmacotherapy

- <8: Minimal – Mild AW, Drug therapy not necessarily indicated
- 8-15: Moderate AW, Drug therapy indicated.
- >15: Severe, Drug therapy absolutely indicated, consider inpatient treatment

http://www.chce.research.va.gov/apps/PAWS/quiz/q1.html

61

Mechanisms Underlying Alcohol Withdrawal

- Multiple neuroadaptive changes in CNS
  - Decreased GABA activity
  - Increased glutamate activity
  - Upregulated calcium channel activity
  - Increased noradrenergic activity
- Alcohol withdrawal is associated with increased CNS activity

CNS=central nervous system; GABA=gamma-aminobutyric acid.

Anton RF, Becker HC, eds. Pharmacotherapy and pathophysiology of alcohol withdrawal. (Handbook of Experimental Pharmacology.) 1995.

62

Case: RR

You apply your knowledge and training through Motivational Interviewing. Your open–ended questions and affirmations reviewed with patient's possibilities set the bases for a good rapport with Mr. RR. As part of the treatment dialogue, you showed Mr. RR. his BP elevation 150/90, CIWA:8, and his scores on the CDT, GGT and AST/ALT. You noted that the values were outside the reference ranges for the tests.

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Case: RR

You then explained, in a direct, yet empathetic manner, the significance of the scores and noted that GGT and AST/ALT levels this high can reflect liver damage and that CDT levels this high usually reflect heavy drinking. Mr. RR then agrees to start an outpatient alcohol treatment program.

64

Treatment Plan

There are several evidence-based options for non-pharmacological treatment that have minimal harms:

- Motivational Enhancement Therapy (MET): manualized psychotherapy based on the principles of motivational interviewing; shown to have a small to medium effect size on achieving abstinence
- Cognitive Behavioral Therapy (CBT): focusing on the relationships between thoughts, feelings, and behaviors; help manage urges and triggers

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Treatment Plan

There are several evidence-based options for non-pharmacological treatment that have minimal harms:

- Medical Management (MM): manualized treatment that provides education and strategies to support abstinence and promote medication adherence
- Community based peer support groups such as Alcoholics Anonymous (AA) and other 12-step programs: helpful in achieving long-term remission but not for replacing formal medical treatment

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Alcohol Detoxification Use of Benzodiazepines

- First line agent (gold standard)
- Loss of inhibition/sedation due to lack of ETOH
- Treatment: Replace the GABA activation (inhibition)
- Benzodiazepines:
  - If hepatic impairment: oxazepam or lorazepam
  - Provide dosing for 24 hour intervals – patient must be re-evaluated before more is provided
    - Vital Signs
    - CIWA-Ar

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Benzodiazepines options

Chlordiazepoxide
- Only available in oral form (PO)
- Longer half life than most benzos (5-30 hrs)

Diazepam
- Lipophilic ⇨ rapid onset of action

Lorazapem
- Available in oral form (PO) and IV
- Half life (12-18 hrs)
- Simple metabolism of hepatic glucuronidation (no active metabolite)
- Ideal for patients with cirrhosis/liver damage and elderly population

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Indications for Outpatient withdrawal treatment

- CIWA <8 or some with CIWA 8 –15
- No hx. of AW seizures/delirium
- No serious medical/surgical problems
- No serious psychiatric/drug hx
- Social support
- Supervision/housing available

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Indications for inpatient withdrawal treatment

- History of DTs or withdrawal seizures
- Alcohol withdrawal severity (CIWA>10) + other criteria (e.g Abnormal lab results, Utox + for other substances)
- Pregnancy
- Major medical/surgical problems
- Inability to tolerate oral medication
- Imminent risk to harm himself and/or others
- Active psychosis or cognitive impairment
- Recurrent unsuccessful attempts at ambulatory detoxification

Muncie HL Jr, Yasinian Y, Oge' L. Am Fam Physician. 2013 Nov 1;88(9):589-95.
Lindsay et al. Journal of Addiction Medicine September 2020

70

Treatment of Mild-Moderate Alcohol Withdrawal CIWA-Ar- 8 to 14

Long-acting Benzodiazepines:

- Chlordiazepoxide (Librium) 50-100 Mg Po Q 6-8 Hrs.
- Diazepam (Valium) 10-20 Mg Po Q 6-8 Hrs.

Short-acting Benzodiazepines:

- Lorazepam (Ativan) 2-4 Mg Po Q 1-4 Hrs.

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Treatment of Severe Alcohol Withdrawal CIWA-Ar > 15

Diazepam 10 mg IV

- Repeat 5 mg IV q 5 Min Until Calm

Lorazepam 4 mg po q 1 hr, PRN

- Moderate To Severe Liver Disease
- Elderly Or Confused Patients
- Very Ill Or Debilitated Patients
- Can Be Given PO, IV Or M

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Alcohol Detoxification

Use of Anticonvulsants

Anticonvulsants Reduce Gaba Activity

- CBZ: Reduced rebound withdrawal & post-detox drinking (Malcolm, 2002)
- Gabapentin normalizes alcohol-induced effects on GABA and glutamate; has no hepatic metabolism
- Gabapentin more effective than lorazepam in reducing post-detox drinking (Myrick, 2009)
- Gabapentin, divalproex & vigabatrin may prove useful
- Caution: CBZ & divalproex have limited use in patients with severe hepatic or hematologic disease

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Alcohol Detoxification

Anticonvulsants Effectiveness and Limitations

Advantages	Disadvantages
• No abuse liability • Cognition • Neuroprotective • Protracted Withdrawal	• Limited clinical experience • Hematological side effects • Liver toxicity

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When to Consider Pharmacotherapy

- Anti-craving Medication as the new standard of care
  - Consider immediately post-detoxification for ALL patients with alcohol use disorder
  - Efficacy requires counseling and/or frequent physician monitoring
- Most FDA approved medications for SUDs can be used in outpatient settings
- Exception: Methadone maintenance therapy: can only be used for treatment of opioid addiction in licensed opioid treatment programs

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Pharmacogenetics in AUD treatment

Medication	Genetic Variant	Outcome Moderated	Notable Studies
Topiramate	*GRIK1* (rs2832407)	Heavy drinking days (%); side effects	Kranzler et al., 2014 (2); Ray et al., 2009 (4)
Naltrexone	*OPRM1* (An40Asp), (rs1799971), DRD4 VNTR	Heavy drinking days (%); abstinence rates; relapse to heavy drinking	Anton et al., 2008 (12); Kim et al., 2009 (13); Oslin et al., 2003 (14); Tidey et al., 2008 (15)
Ondansetron	LL/LS/SS (5-HTTLPR) (rs1042173), *SLC6A4* (5-HTTLPR)	Drinks per drinking day; days abstinent (%)	Johnson et al., 2011 (9)
Sertraline	5-HTTLPR triallelic *SLC6A4*	Heavy drinking days (%); drinking days (%)	Kranzler et al., 2011 (8)
Acamprosate	*GATA4* (rs1327367)	Relapse	Kiefer et al., 2011 (10)
Disulfiram	*DBH* (rs1611115)	Adverse events	Mutschler et al., 2012 (11)

Note: OPRM 1 predictive value for NTX response has not been supported (Schacht, J., Randall, P., Latham, P. *et al* 2017)

Batki & Pennington (2014) Am J Psychiatry
Hartwell and Kranzler (2019)Expert Opinion on Drug Metabolism & Toxicology

76

Alcohol Use Disorder (Relapse Prevention) FDA Approved

- Naltrexone (Revia): 1994
- Long Acting Naltrexone IM (Vivitrol): 2006

→ Binge drinking

- Acamprosate (Campral): 2004 → Maintain abstinence
- Disulfiram (Antabuse): 1949 → With supervision improve treatment adherence
- Nalmefene (2016) *European Medicines Agency (EMA)*

→ Heavy drinking days

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Neurochemical Targets for AUD

Phenomenon	Neurochemistry	Pharmacotherapy
Reward	Opioids Glutamate 5-HT3 Nicotinic cholinergic	**Naltrexone*** **Acamprosate*** Topitamate, Ondasetron, Varenicline
Protracted withdrawal/dysphoria/ anxiety	Glutamate GABA	**Acamprosate *** Topiramate, Gabapentin, Baclofen
Impulsivity	Glutamate Opioids DA	Topiramate? Naltrexone?

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Pharmacotherapy of Alcohol Use Disorder:
Naltrexone-oral/Mechanism of Action

- Reduces positive reinforcement (reward craving)
  - Potent inhibitor at mu opioid receptors
- Modulates the mesolimbic dopamine system in the VTA & projections to the nucleus accumbens
- There is mixed evidence around markers that predict a favorable response to naltrexone treatment, such as:
  - Male sex
  - A positive family history of alcoholism
  - High levels of craving,
  - Polymorphism (asp variant) of the opioid receptor gene OPRM1?

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Pharmacotherapy of Alcohol Use Disorder:
Naltrexone-oral/Mechanism of Action

- The patient does not experience the full euphorogenic/reinforcing effect of alcohol.
  - suppresses/reduces endogenous opioids (beta-endorphin) involved in the reinforcing (pleasurable) and subsequent reduces DA in NAc effects of alcohol and possibly craving
- Prevents a slip from becoming a full-blown relapse

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Pharmacotherapy of Alcohol Use Disorder:
Naltrexone-oral / Effectiveness

- Effective in reducing relapse to heavy drinking.
- A meta-analysis of (N:16 studies and 2347 patients) found a:
  - risk decrease (RD) for a return to any drinking
  - (risk decrease = −0.05; 95% CI, −0.10 to −0.002; number needed to treat = 20)
- (19 studies N: 2875) found also a:
  - risk decrease (RD) of binge drinking
  - (risk decrease = −0.09; 95% CI, −0.13 to −0.04; number needed to treat = 12)
- Medication compliance may be a limiting factor in oral treatment.

Kranzler Hr et al JAMA 2018 ; Srisurapanont M, Jarusuraisin N. Cochrane Database Syst Rev 2005;(1):CD001867.

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Pharmacotherapy of Alcohol Use Disorder:
Naltrexone-oral / Dosing and Safety

Oral Naltrexone Hydrochloride
- FDA approved dose: 50 mg per day
- Antagonist of mu , delta and kappa opioid receptors.
- Antagonizes opioid-containing agents, but no other significant drug-drug interactions.

- Some have used 100 mg daily with rationale that naltrexone has been effective for heroin addiction at doses of 100mg-100mg-150 mg q Monday, Wednesday, and Friday; an effective plasma concentration can be obtained even if some doses are missed

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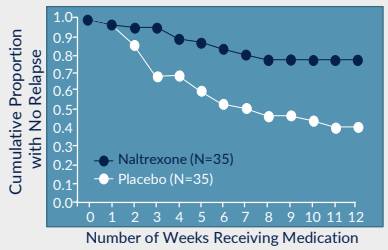
Pharmacotherapy of Alcohol Use Disorder:
Naltrexone-oral /Dosing and Safety

- Side effects
  - GI: abdominal pain, diarrhea, decreased appetite, nausea
  - Sedation: daytime sleepiness, fatigue, insomnia, headache
- Reversible hepatoxicity
  - LFT's should be monitored closely
- Works best with complaint patients
  - Requires counseling (CBT) or frequent MD monitoring visits (Project Combine, 2006)
  - Efficacy questioned in women (O'Malley, 2007)

Physician's Desk Reference (www.PDR.net) and Epocrates. Accessed on September 1, 2011.

83

Naltrexone-Oral in the Treatment of Alcohol Use Disorder



Volpicelli et al., Arch Gen Psychiatry, 1992

84

Pharmacotherapy of Alcohol Use Disorder:

Long-Acting Naltrexone (IM)

Extended-Release - Injectable Naltrexone

- 1 injection per month/ 380 mg
- 100 µm diameter microspheres of naltrexone and polymeric matrix.

- Advantages: once a month injection can be done in clinician's office
- Better adherence with once monthly dosing
- More stable plasma concentrations compared to the oral formulation

Garbutt et al. JAMA. 2005;293:1617-1625. Physician's Desk Reference (www.PDR.net) and Epocrates. Accessed on September 1, 2012.

85

Pharmacotherapy of Alcohol Use Disorder:

Long-Acting Naltrexone (IM) Dosing and Safety

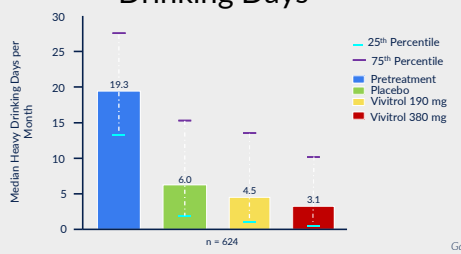
Extended-Release Injectable Naltrexone

- Side effects: nausea & headaches; more sedation than with the oral formulation
- LFT's should be monitored closely
- Injection site reactions possible
- Best results in patients sober 1 week prior to starting the medication
- Efficacy shown in more severe alcoholics
- Reduction in heavy-drinking days (48.9% vs 30.9% on placebo)

Pettinati HM, Alcohol Clin Exp Res, May 2011

86

Naltrexone-injectable in the Treatment of Alcohol Use Disorder Results: Heavy Drinking Days



Garbutt et al., 2005

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Protracted Withdrawal Symptom

- Sleep dysregulation
- Irritability
- Mood instability
- Anxiety

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Pharmacotherapy of Alcohol Use Disorder:
Acamprosate/ Mechanism of Action

- Stabilizes glutamatergic neurotransmission altered during withdrawal (Littleton 1995).
- Chronic ETOH exposure alters GABA & NMDA systems
  - Restores balance between inhibitory & excitatory neurotransmission
- Anticraving, reduced protracted withdrawal
- Reduce negative reinforcement (abstinence craving)
- No abuse liability, hypnotic, muscle relaxant, or anxiolytic properties

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Pharmacotherapy of Alcohol Use Disorder:
Acamprosate/ Effectiveness

- Effective in improving abstinence.
- A meta-analysis (16 studies; N = 4847) concluded that acamprosate treatment was associated with a greater reduction than placebo in the risk of drinking among abstinent patients but no reduction in the likelihood of binge drinking.
  - (risk decrease = −0.09; 95% CI, −0.14 to −0.04; number needed to treat = 12)
- The US trial showed efficacy only in patients motivated for abstinence.

Jonas et al Jama 2014; Kranzler HR, Gage A. Am J Addict. 2008;17:70-76. Mason BJ et al. J Psychiatr Res. 2006;40:383-93.

90

Pharmacotherapy of Alcohol Use Disorder:
Acamprosate/Dosing and Safety

- 666 mg three times a day (2000 mg daily)
- Excreted by the kidneys; no liver metabolism
- Contraindicated: significant renal disease with creat cl <30ml/min or those who are pregnant
- Mild diarrhea (16% acamprosate vs. 10% placebo)
- Recommendation: patients with hepatic disease or those treated with opioids. Advantage when a patient is taking multiple medications
- No drug-drug interactions.

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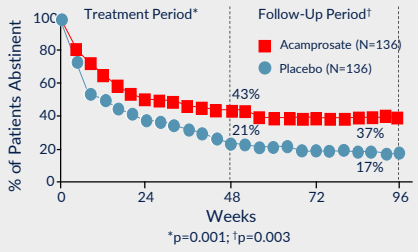
Acamprosate in the Treatment of Alcohol Use Disorder

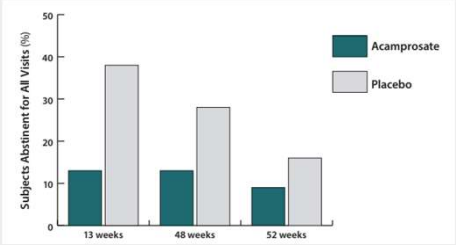


*p=0.001; †p=0.003

Sass et al., Arch Gen Psychiatry, 1996

92

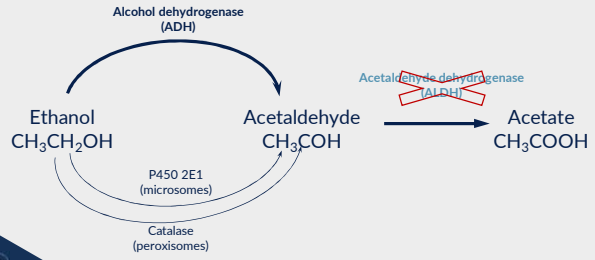
Acamprosate in the Treatment of Alcohol Use Disorder



Kranzler HR, Gage A. Acamprosate efficacy in alcohol-dependent patients: summary of results from three pivotal trials. Am J Addict. 2008;17(1):70–6.

93

Pharmacotherapy of Alcohol Use Disorder:
Disulfiram Mechanism of Action



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Pharmacotherapy of Alcohol Use Disorder:
Disulfiram/ Mechanism of Action

- Alcohol → Acetaldehyde → Acetate
- Disulfiram irreversibly binds to acetaldehyde dehydrogenase inhibiting the metabolism of acetaldehyde to acetate.
- Acetaldehyde accumulates resulting in a very unpleasant reaction (tachycardia, headache, nausea, vomiting, flushing).

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Pharmacotherapy of Alcohol Use Disorder:
Disulfiram Effectiveness

- Second Line Treatment
- In a meta-analysis of 22 studies was associated with:
  - Sustained abstinent compared to control conditions only in open-label studies
- Double-blind, placebo-control study design is not helpful as both the medication and the placebo pills may (or may not) result in fear of drinking.
- Most studies are negative, but disulfiram may be helpful for a better response than control conditions when medication adherence was supervised

Diehl et al. Alcohol Alcohol. 2010;45:271-277. Fuller RK et al. JAMA. 1986;256:1449-55. Kranzler HR, Soyka M. Diagnosis and Pharmacotherapy of Alcohol Use Disorder: A Review. JAMA. 2018;320(8):815-824

96

Pharmacotherapy of Alcohol Use Disorder:
Disulfiram Dosing and Safety

- 250-500 mg daily.
  - First dose 12 hours after the last drink;
  - 500mg PO each morning for 1-2 weeks, then 250mg PO each morning
- Some liver toxicity; monitor LFTs. Caution with CAD. Contraindicated: psychosis, significant liver disease, esophageal varices, pregnancy, impulsivity (Barth et al., 2010)
- Inhibits hepatic microsomal enzymes and increases drug levels (phenytoin, warfarin, isoniazid, metronidazole, TCA and benzodiazepines among others)
- SIDE EFFECTS: skin/acneiform eruptions, drowsiness, headache, metallic taste, decreased libido/potency

Physician's Desk Reference (www.PDR.net) and Epocrates. Accessed on March 1, 2018.

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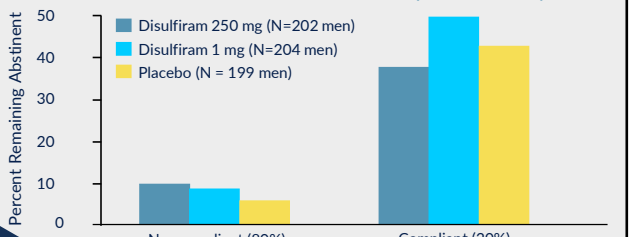
Disulfiram in the Treatment of Alcohol Dependence
Disulfiram and Abstinence Rates (VA Cooperative Study)



Fuller RK et al. JAMA. 1986; 256:1449-1455

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MAT + FDA Approved

Medication (typical dose)	Mechanism of action	Adverse effects	Cautions	Lab monitoring	Other
*Naltrexone (50-100mg PO daily or 380mg IM monthly)	Blocks opioid receptors May reduce rewarding effects of alcohol	Nausea Headache, dizziness, insomnia Anxiety *Injection site reaction	Need 7-10 days *opioid free* if patient previously receiving chronic opioids Do not use if: Current opioid use LFTs ≥ 5x upper limit of normal	LFTs prior and during treatment	Number needed to treat to reduce heavy drinking days is 12
*Acamprosate (666mg PO three times daily)	Levels out GABA + glutamate activity	Diarrhea	CrCl 30-50 mL/min: 333mg PO three times daily Do not use if: CrCl ≤ 30 mL/min	Renal function (basic metabolic panel) prior and during treatment	Prolongs periods of abstinence
*Disulfiram (250-500mg PO daily)	Blocks acetaldehyde dehydrogenase Blocks enzyme involved in dopamine metabolism	Disulfiram-alcohol reaction if combined Rare but notable: acute liver failure	Need ≥ 12h alcohol abstinence Many medication interactions Do not use if: Severe cardiac disease or coronary occlusion Primary psychotic disorder	LFTs prior and during treatment	Daily observed disulfiram Targeted disulfiram (e.g. weddings, reunions, holidays)

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Combinations

- Naltrexone and acamprosate have different mechanisms of action and may work synergistically on cravings:
  - Naltrexone on positive reinforcement
  - Acamprosate on negative reinforcement
- Medications and psychotherapy.

Rosner S et al. J Psychopharmacol. 2008;22:11-23.

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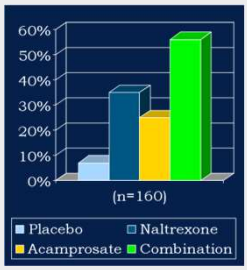
Naltrexone/Acamprosate



- Abstinence rates during a 12-week trial with:
  - Naltrexone 50 mg QD,
  - Acamprosate 666 mg TID.
- The combination of the two medications helped alcoholics stay abstinent (P=0.002) better than each drug alone.

Adapted from Kiefer F et al. Arch Gen Psychiatry. 2003;60:96.

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Project MATCH

- Compared outcome efficacy for patients matched to treatments based on a prior hypotheses about 11 client attributes
- Treatment was for 12 weeks; follow-ups continued for years
- 12-Step programs, CBT and MET were compared
- Each of the three methods helped in the treatment of alcoholism
  - However outpatients who received TSF were more likely to remain abstinent after 1 year following treatment
- There were a few matching effects, and they were weak

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The COMBINE Study

- 1383 patients with alcohol dependence randomized to varying combinations of oral Naltrexone, Acamprosate, combined behavioral intervention (CBI) and medical management (MM)
- Patients received naltrexone, acamprosate, both, or neither
- Half of patients received psychotherapy in addition to medical management
- One patient cohort received psychotherapy alone, no pills

JAMA. 2006;295:2003-2017.

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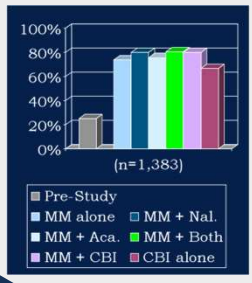
The COMBINE Study



- Percentage of abstinent days per month during a 16-week treatment trial with:
  - Naltrexone 100 mg QD,
  - Acamprosate 1 g TID.
- All treatment groups had an increase in % days abstinent. Overall effect was from 25% to 73%.

Adapted from Anton et al. JAMA. 2006;295:2003-2017.

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The NIAAA COMBINE Study Results

- For patients receiving MM, naltrexone, or CBI therapy, improved outcomes over placebo plus MM
  - Naltrexone + MM had the best outcome
- Acamprosate did not add benefit to naltrexone or CBI, and was no more effective than placebo plus MM
- Taking tablets and seeing a health care professional was more effective than receiving CBI alone (possible placebo effect)
- One-year outcome: no significant differences among the groups

Adapted from Anton et al. JAMA. 2006;295:2003-2017.

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Other Pharmacological Agents

Anticonvulsants
- Topiramate
- Gabapentin
- Carbamazepine
- Valproic Acid

GABA agonist
- Baclofen

Alpha1 adrenergic blocker
- Doxazosin
- Prazosin

Alpha 2 agonists
- Clonidine

Serotonin (5-HT3) antagonists
- Ondansetron
- Mirtazapine

Selective Serotonin Reuptake Inhibitors

Partial agonist for the α4β2 nicotinic acetylcholine receptor subtype (nACH)
- Varenicline

Mu and delta opioid antagonist and partial kappa agonist
- Nalmefene

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Conclusions

- Identify the need of your patients to get treatment
- Substance use disorders are chronic, be ready for relapses
- Prevention is based on screening and early Intervention
- CIWA-Ar is your best ally for AWS
- AWS=BZD most effective, safest and cheapest treatment
- Medications for Alcohol Use Disorder are relatively safe but modestly effective
- Naltrexone is best for "cutting down."
- Acamprosate is best for preventing "the first drink."
- Pharmacotherapy and psychotherapy modalities can be offered by you
- Pharmacotherapy and psychotherapy modalities are effective and scientifically based approaches

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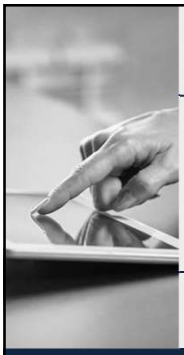

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JULY 2023 REVIEW COURSE 2023

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