

ASAM REVIEW COURSE 2023

**Alcohol Use Disorder:
Neurobiology, Diagnosis
and Treatment**

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1

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2

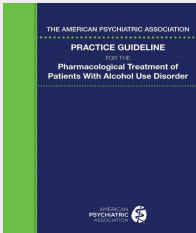
Outline

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 Pharmacotherapy and Psychotherapy
10. New Directions
11. Conclusion

3

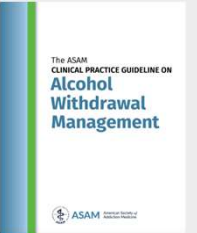
APA Practice Guideline for the Pharmacological Treatment of Patients With Alcohol Use Disorder

December 2017




ASAM Clinical Practice Guideline on Alcohol Withdrawal Management

January 2020



4


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 bit 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: "drunkenness 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..."

5

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.



6

Case: RR

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

- Depression
- Insomnia
- Irritability and anxiety



7

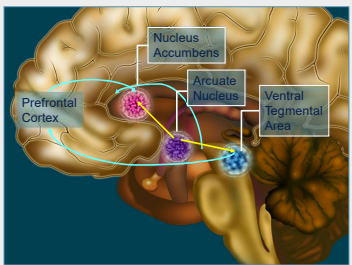
Case: RR

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.



8

Alcohol Use Disorder a Disease?

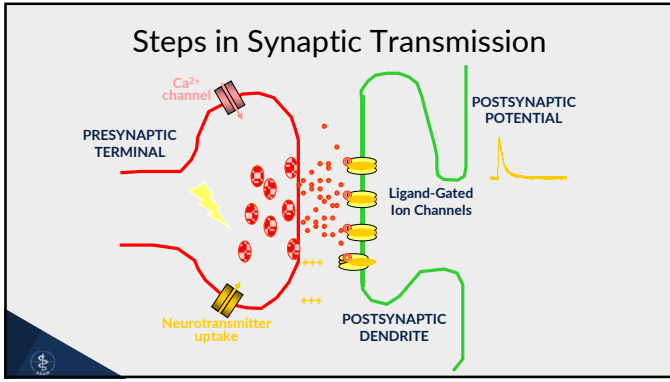


9

Neurotransmitter Systems

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

10



11

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).

12

Case: RR

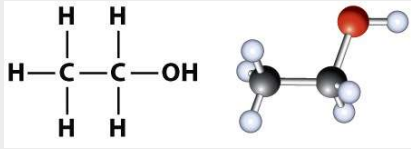
Substance abuse h/x and symptoms
His last drink was the previous night. He explained he often has **diarrhea and shakes in the morning**, which he attributes to "anxiety" because these symptoms are **alleviated with 1 or 2 alprazolam** that has been prescribed by his PCP for the past decade.

No other drugs or substance use history.



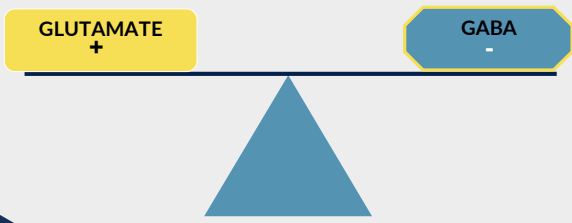
13

Alcohol (Ethanol C2 O1 H6)

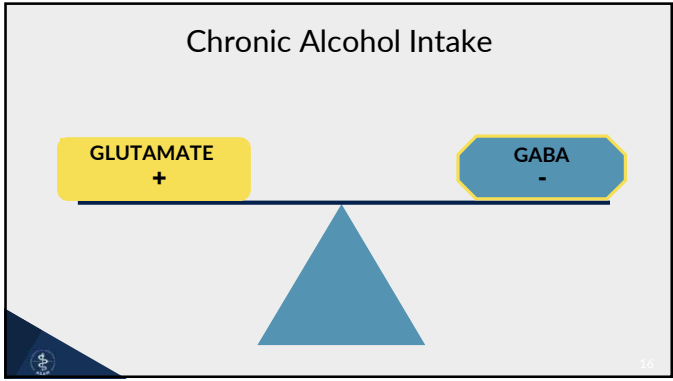


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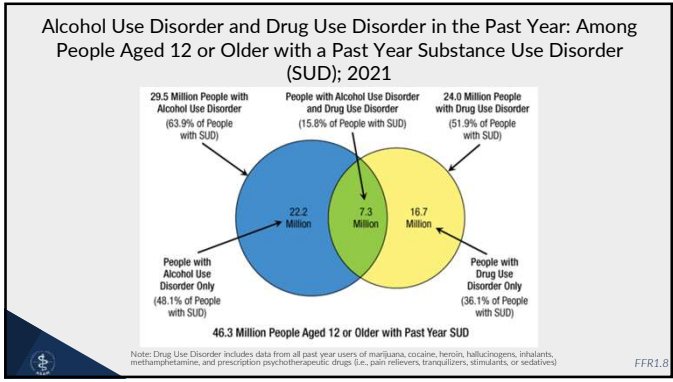
Acute Alcohol Intake



15



16



17

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)

18

Cost and Scope of Alcohol-Related Problems

Cost to Society

Billions of dollars

Category	Billions of dollars
Alcohol	249
Illicit drugs	193
Tobacco	295
Cancer	216.6
HIV/AIDS	36

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

19

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

U.S. Prevalence of Alcohol Use Disorder

Legend: 12-month (blue), Lifetime (purple)

Severity	12-month (%)	Lifetime (%)
Mild	~5	~10
Moderate	~5	~10
Severe	~5	~10
Any AUD	~14	~29

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)

20

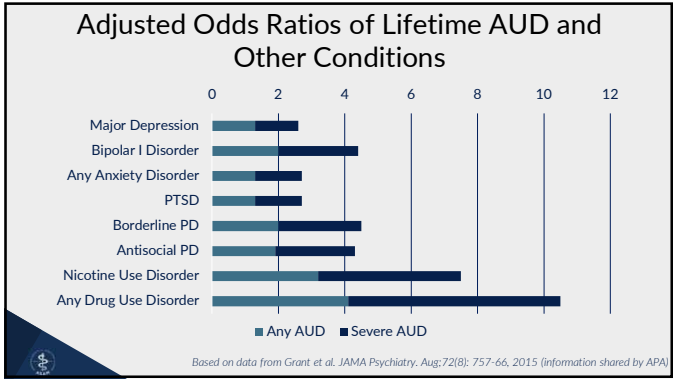
Epidemiology/Demographics

AUD affects individuals of all demographic groups

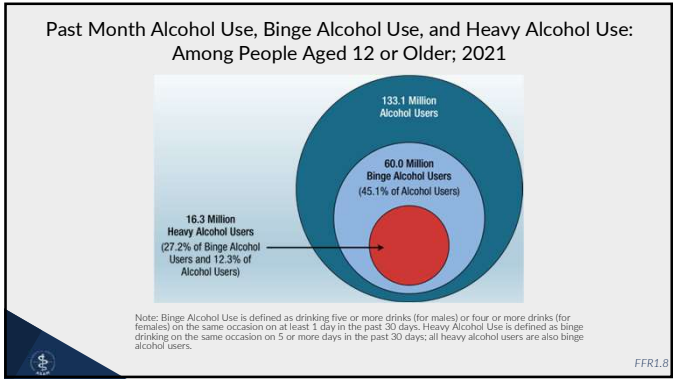
- Onset: 18-29 years
- Ethnicity (12-month prevalence):
 - American Indian/Alaska Native 19.2%
 - African American 14.4%
 - White 14%
 - Hispanic 13.6%
 - Asian-American/Pacific Islander 10.6%
- Gender (12-month prevalence):
 - Men 17.6%
 - Women 10.4%

Grant et al. 2015

21



22



23

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

24

How Much is "too much"?

Heavy Drinking	Binge Drinking	Emerging Trend-High Intensity Drinking
<ul style="list-style-type: none">• 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.)	<ul style="list-style-type: none">• 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	<p>Consuming ETOH at levels that are two or more times the gender-specific binge drinking thresholds</p> <p>10 or more standard drinks (or alcoholic drink equivalents) for males and 8 or more for females</p>

25

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

26

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	2013
<ul style="list-style-type: none">• 65.4% Past Year Drinking• 21.5 % Monthly Binge Drinking	<ul style="list-style-type: none">• 72.7% Past Year Drinking• 25.8 % Monthly Binge Drinking

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

27

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

28

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

29

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

30

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

31

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

32

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

33


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).



34

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




35

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




36

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.



37


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



38

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



39

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

40

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."

41

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 drink 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

Severity

Abstinence or Low-risk Drinking

AUDIT-C = 0-3

Health promotion

Moderate-risk Drinking

AUDIT-C = 4-5

Brief intervention

High-risk Drinking

AUDIT-C = 6-7

Brief intervention
+/- Pharmacotherapy
+/- Psychosocial interventions

Severe-risk Drinking

AUDIT-C = 8-9

Pharmacotherapy
+/- Psychosocial interventions
+/- Specialty care management

Severe-risk Drinking

AUDIT-C = 10-12

Specialty care management

42

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.

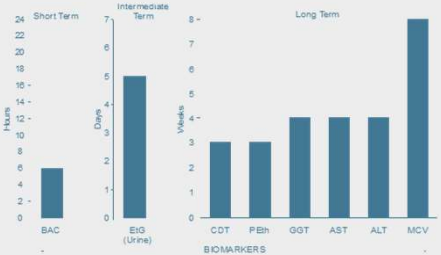
43

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)

44

Window of Assessment for Various Alcohol Biomarkers



45

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 (>40g/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

46

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

47

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.



48

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

49

Introduction Alcohol Withdrawal

Epidemiology

Neurobiology

- Neurotoxicity
- Kindling

Management of Alcohol Withdrawal

- Benzodiazepines
- Anticonvulsants

Real World Implications

- Outpatient vs. Inpatient
- Evaluation and Management

50

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%

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

51

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

52

Managing Alcohol Withdrawal

Principles of treatment

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

53

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

54

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




55

States of AWS

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


There is not necessarily a linear progression.



56

States of AWS

<p>Autonomic Hyperactivity</p> <ul style="list-style-type: none"> • Clear Sensorium • Tremulous • Diaphoresis • Anxiety • Nausea/Vomiting • Increase catecholamines in urine, serum and CSF • Start 6 hrs after last drink Peak 24-48 hrs 	<p>Hallucinations</p> <ul style="list-style-type: none"> • Most common= VISUAL <p>Neuronal excitation</p> <ul style="list-style-type: none"> • Seizures (Generalized Tonic – Clonic) • Up to 10% • Most common in first 24 - 48 hours after last drink
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57

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

58

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

59

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.) 1993.

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.



63

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

65

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

66

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

67

Benzodiazepines options

Chlordiazepoxide

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

Diazepam

- Lipophilic → rapid onset of action

Lorazepam

- 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

Benzodiazepines: Withdrawal Assessment Scale for Alcohol (Revised) (CIWA-Ar)

<p>Alcohol withdrawal symptoms</p> <p>1. Tremor of outstretched hands</p> <p>2. Parosmia (distorted taste)</p> <p>3. Tachycardia (heart rate > 100)</p> <p>4. Spontaneous nystagmus (eye movement and tearing)</p> <p>5. Hyperreflexia (exaggerated gag reflex)</p> <p>6. Diaphoresis (sweating)</p> <p>7. Blood pressure > 160/90 mmHg</p> <p>8. Altered mental status</p> <p>9. Convulsions</p> <p>10. Delirium</p> <p>11. Seizures</p> <p>12. Hypotension</p> <p>13. Hypothermia</p>	<p>CIWA-Ar score</p> <p>0 = None</p> <p>1 = Mild</p> <p>2 = Moderate</p> <p>3 = Severe</p> <p>4 = Very severe</p> <p>5 = Life threatening</p> <p>6 = Fatal</p> <p>7 = Death</p> <p>8 = Death</p> <p>9 = Death</p> <p>10 = Death</p>
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68

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

69

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.

71

**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

72

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

73

Alcohol Detoxification

Anticonvulsants Effectiveness and Limitations

Advantages	Disadvantages
<ul style="list-style-type: none"> • No abuse liability • Cognition • Neuroprotective • Protracted Withdrawal 	<ul style="list-style-type: none"> • Limited clinical experience • Hematological side effects • Liver toxicity

74

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

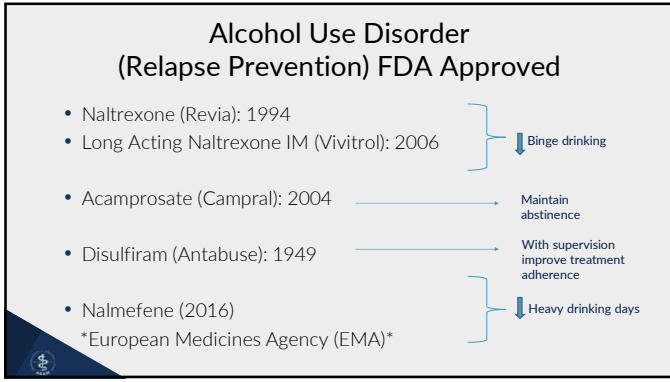
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Pharmacogenetics in AUD treatment

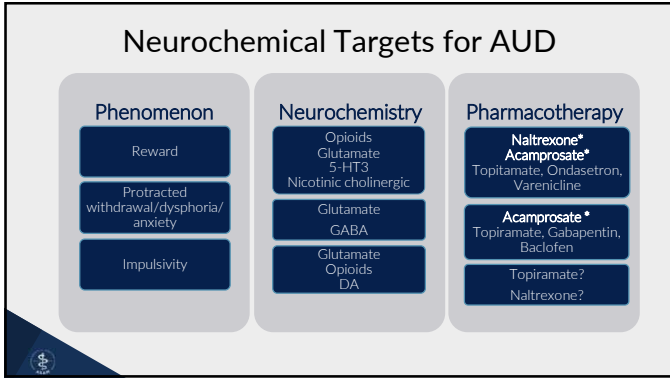
Medication	Genetic Variant	Outcome Moderated	Notable Studies
Topiramate	GRK1 (rs882497)	Heavy drinking days (%); side effects	Kranzler et al., 2014 (3); Ray et al., 2009 (4)
Naltrexone	OPRM1 (A1140A), (rs179997), DRD4 VNTR	Heavy drinking days (%); abstinence rates; relapse to heavy drinking	Anton et al., 2008 (12); Kim et al., 2009 (13); Oslin et al., 2003 (14); Tidey et al., 2008 (15)
Ondansetron	5-HTTLPR (rs1042773), 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 (rs16115)	Adverse events	Mutschler et al., 2012 (11)

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

76



77



78

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?

79

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

- The patient does not experience the full euphrogenic/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

80

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):CD001847

81

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

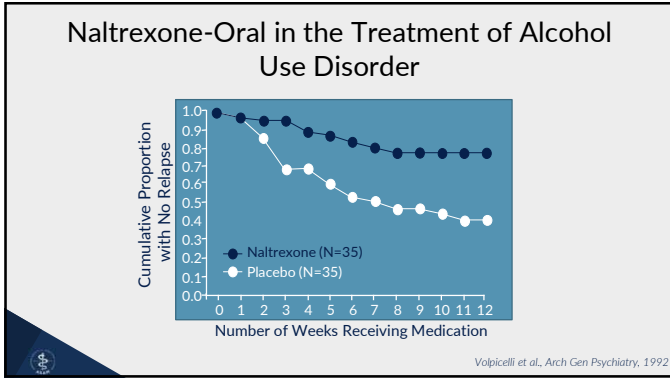
82

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 hepatotoxicity
 - LFT's should be monitored closely
- Works best with compliant 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



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.

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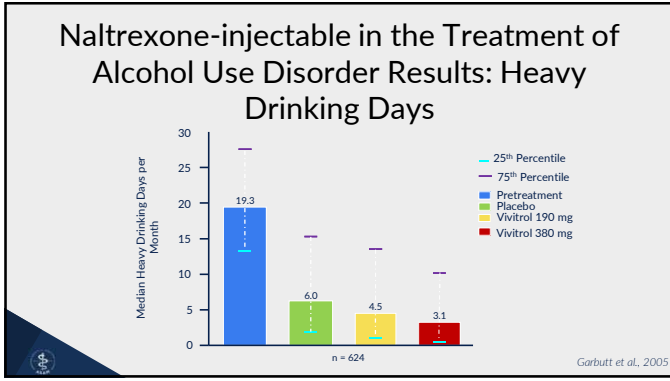
Pharmacotherapy of Alcohol Use Disorder:
Long-Acting Naltrexone (IM) Dosing and Safety

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



87

Protracted Withdrawal Symptom


- Sleep dysregulation
- Irritability
- Mood instability
- Anxiety



88

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




89

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.

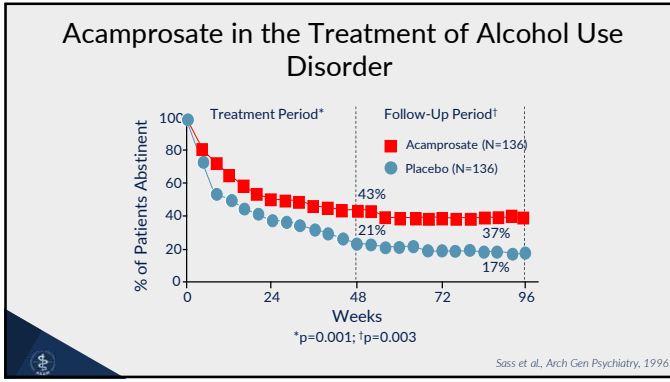


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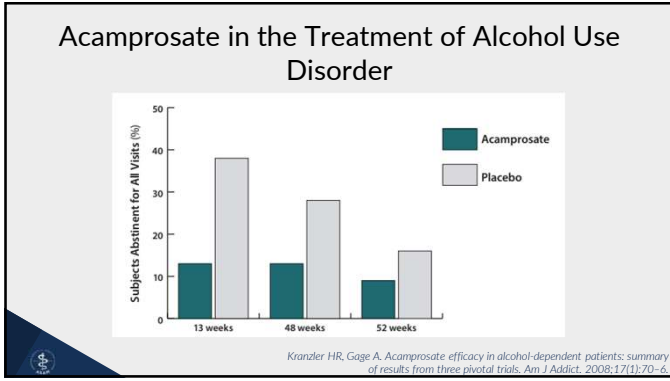
Pharmacotherapy of Alcohol Use Disorder: Acamprosate/Dosing and Safety

- 666 mg three times a day (2000 mg daily)
- Excreted by the kidneys; no liver metabolism
- Contraindicated: significant renal disease with creatinine <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.

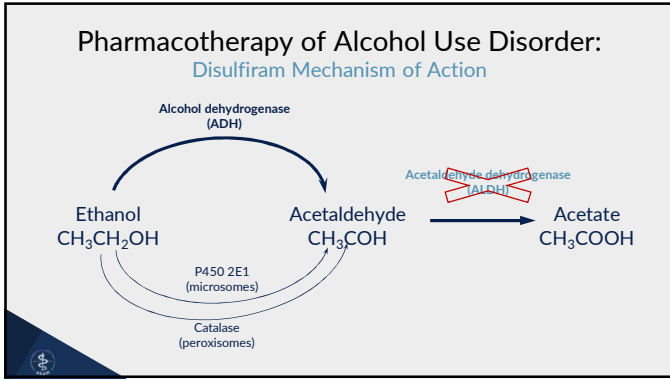
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92



93



94

- 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).

95

- 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

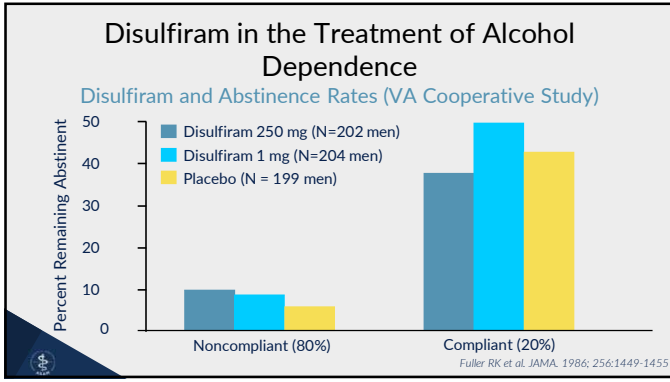
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Pharmacotherapy of Alcohol Use Disorder: Disulfiram Dosing and Safety

- 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.

97



98

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	Diarhea	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 > 12% 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)

99

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.

100

Naltrexone/Acamprosate

Treatment	Abstinence Rate (%)
Placebo	~10%
Naltrexone	~35%
Acamprosate	~28%
Combination	~55%

- 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.

101

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

102

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

103

The COMBINE Study

Group	Percentage of Abstinent Days
Pre-Study	25%
MM alone	~70%
MM + Nal.	~70%
MM + Aca.	~70%
MM + Both	73%
MM + CBI	~70%
CBI alone	~70%

- 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.

104

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.

105

Other Pharmacological Agents


<p>Anticonvulsants</p> <ul style="list-style-type: none"> • Topiramate • Gabapentin • Carbamazepine • Valproic Acid <p>GABA agonist</p> <ul style="list-style-type: none"> • Baclofen <p>Alpha1 adrenergic blocker</p> <ul style="list-style-type: none"> • Doxazosin • Prazosin 	<p>Alpha 2 agonists</p> <ul style="list-style-type: none"> • Clonidine <p>Serotonin (5-HT3) antagonists</p> <ul style="list-style-type: none"> • Ondansetron • Mirtazapine <p>Selective Serotonin Reuptake Inhibitors</p> <p>Partial agonist for the $\alpha 4\beta 2$ nicotinic acetylcholine receptor subtype (nACh)</p> <ul style="list-style-type: none"> • Varenicline <p>Mu and delta opioid antagonist and partial kappa agonist</p> <ul style="list-style-type: none"> • Nalmefene
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106

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

107



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108
