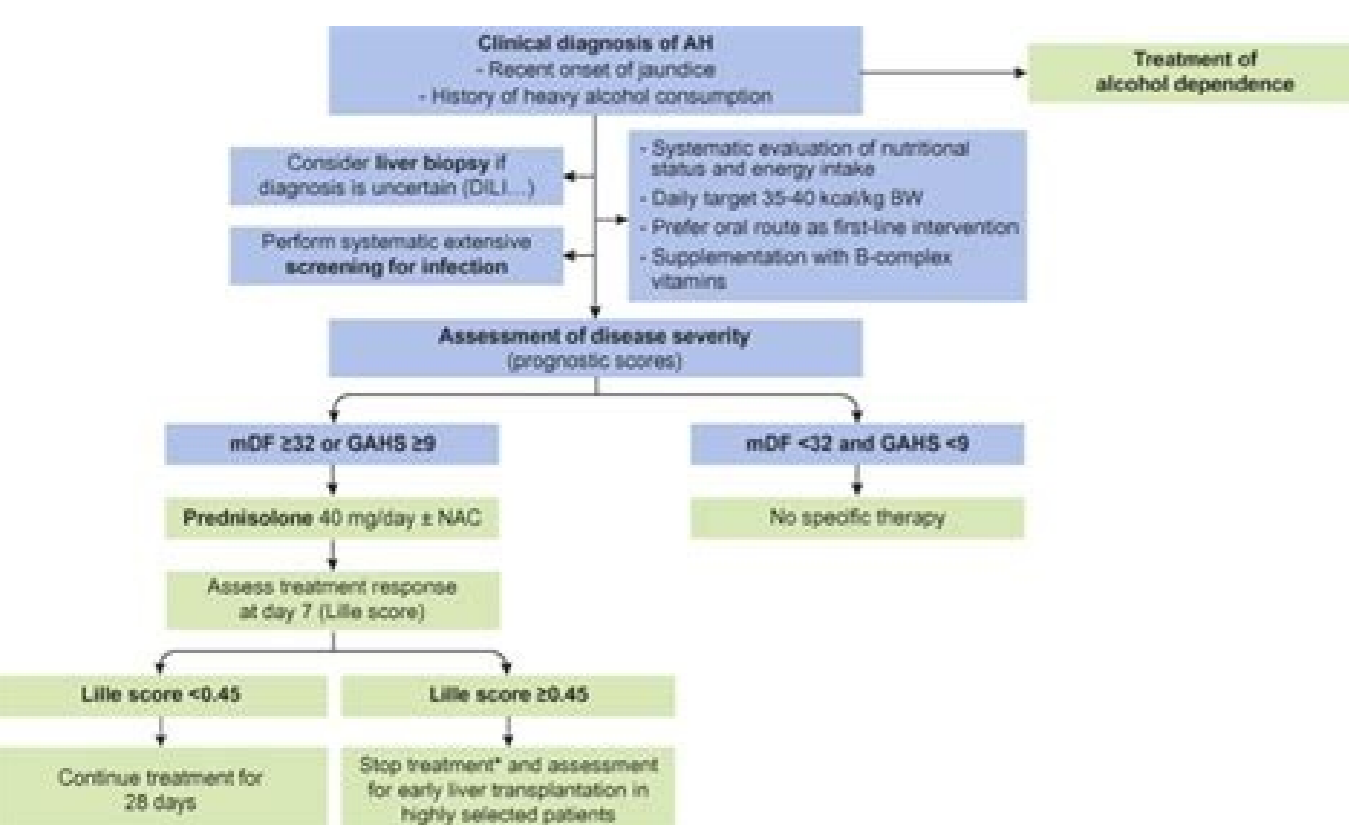


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SCIENCE ADVANCES | REVIEW

DISEASES AND DISORDERS
Advances in the science and treatment of alcohol use disorder

K. Witkiewitz¹, R. Z. Litten², L. Leggio^{3,4,5,6}

Alcohol is a major contributor to global disease and a leading cause of preventable death, causing approximately 88,000 deaths annually in the United States alone. Alcohol use disorder is one of the most common psychiatric disorders, with nearly one-third of U.S. adults experiencing alcohol use disorder at some point during their lives. Alcohol use disorder also has economic consequences, costing the United States at least \$249 billion annually. Current pharmaceutical and behavioral treatments may assist patients in reducing alcohol use or facilitating alcohol abstinence. Although recent research has expanded understanding of alcohol use disorder, more research is needed to identify the neurobiological, genetic and epigenetic, psychological, social, and environmental factors most critical in the etiology and treatment of this disease. Implementation of this knowledge in clinical practice and training of health care providers is also needed to ensure appropriate diagnosis and treatment of individuals suffering from alcohol use disorder.

INTRODUCTION

In most regions of the world, most adults consume alcohol at least occasionally (1). Alcohol is among the leading causes of preventable death worldwide, with 7 million deaths per year attributable to alcohol. In the United States, more than 55% of those aged 26 and older consumed alcohol in a given month, and one in four adults in this age group engaged in binge drinking (defined as more than four drinks for women and five drinks for men on a single drinking occasion) (2). Excessive alcohol use costs U.S. society more than \$200 billion annually and is the fifth leading risk factor for premature death and disability (3).

The morbidity and mortality associated with alcohol are largely due to the high rates of alcohol use disorder in the population. Alcohol use disorder is defined in the *Diagnostic and Statistical Manual for Mental Disorders*, 5th edition (DSM-5) (4) as a pattern of alcohol consumption, leading to problems associated with 2 or more of 11 potential symptoms of alcohol use disorder (see Table 1 for criteria).

In the United States, approximately one-third of all adults will meet criteria for alcohol use disorder at some point during their lives (5), and approximately 15.1 million U.S. adults meet criteria for alcohol use disorder in the previous 12 months (6). The public health impacts of alcohol use extend far beyond those individuals who drink alcohol, engage in heavy alcohol use, and/or meet criteria for an alcohol use disorder. Alcohol use is associated with increased risk of accidents, workplace productivity losses, increased medical and mental health costs, and greater rates of crime and violence (7). Analyses that take into account the overall harm due to drugs (harm to both users and others) show that alcohol is the most harmful drug (7).

Only a small percent of individuals with alcohol use disorder contribute to the greatest societal and economic costs (8). For example, in the 2015 National Survey on Drug Use and Health survey (total n = 43,561), a household survey conducted across the United States, 11.8% met criteria for an alcohol use disorder (n = 5120) (6). Of these 5124 individuals, 67.4% (n = 3455) met criteria for a mild disorder (two or three symptoms, based on DSM-5), 18.8% (n = 964) met criteria for a moderate disorder (four or five symptoms, based on DSM-5), and only 13.8% (n = 705) met criteria for a severe disorder (six or more symptoms) (6). There is a large treatment gap for alcohol use disorder, arising from the fact that many individuals with alcohol use disorder do not seek treatment. Those with a mild or moderate alcohol use disorder may be able to reduce their drinking in the absence of treatment (9) and have a favorable course; but it is those with more severe alcohol use disorder who most often seek treatment and who may experience a chronic relapsing course (10).

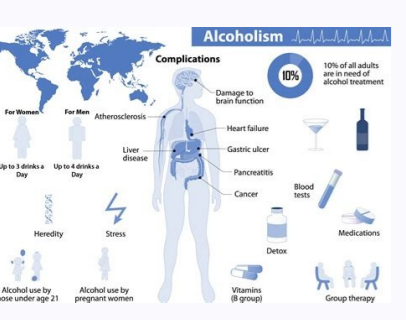
HISTORY OF TREATMENT FOR ALCOHOL USE DISORDER

Near the end of the 18th century, the Pennsylvania physician Benjamin Rush described the loss of control of alcohol and its potential treatments (11). His recommendations for remedies and case examples included practicing the Christian religion, experiencing guilt and shame, pairing alcohol with aversive stimuli, developing other passions in life, following a vegetarian diet, taking an oath to not drink alcohol, and sudden and absolute abstinence from alcohol. Through the 1800s and early 1900s, the temperance movement laid the groundwork for mutual help organizations, and the notion of excessive alcohol use as a moral failing. During the same period, inebriate asylums emerged as a residential treatment option for excessive alcohol use, although the only treatment offered was forced abstinence from alcohol (12). The founding of Alcoholics Anonymous (A.A.) in the 1930s (13) and the introduction of the modern disease concept of alcohol use disorder (previously called "alcoholism") in the 1940s (14) laid the groundwork for many of the existing treatment programs that remain widely available today. Over the past 80 years, empirical studies have provided support for both mutual support (A.A. and other support groups, such as SMART [Self-Management and Recovery Training]) and medical models of treatment for alcohol use disorder, as well as the development of new pharmacological and behavioral

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New York State Clinical Education Initiative
Hepatitis C and Drug Use Health Center of Excellence
PRESENTS

Treatment of Alcohol Use Disorder: Clinical Practice Guidelines for the Primary Care Setting

Learning Objectives:

1. Identify alcohol-related and alcohol use disorder among a patient population.
2. Discuss evidence-based treatments for alcohol use disorder.
3. Describe a harm-reduction approach to treatment of alcohol use disorder.

Dr. K. Witkiewitz

Faculty Member, NIDDK
Professor, Division of Intramural Clinical and Biological Research, National Institute on Alcohol Abuse and Alcoholism

Thursday, March 4, 2021
10:00 AM - 12:00 PM

Register Here!

Questions?

Screening, Brief Intervention and Referral to Treatment (SBIRT)

"The 5-minute talk"

The Brief

Get consent to discuss addiction, screen for other substances, ensure safety (suicidal ideation)

STEP 01



STEP 02

The Review

Review low risk drinking guidelines with the patient.

The Link

Express concern. Review link between alcohol and the ED visit. Review link between alcohol use and health outcome

STEP 03



Motivate

"On a scale of 1 to 10 how ready are you to make a change?"

Follow up: "Why did you choose (state patient's chosen number) and not (lower number)?"

STEP 04

The Negotiation

Discuss what patient would like to do.

Include in this plan an opportunity to connect to a treatment resource in the community.

STEP 05



How is alcohol use disorder treated. Asam alcohol use disorder treatment guidelines. Alcohol use disorder treatment guidelines canada. Can medicine help with alcohol use disorder.

The guideline describes the critical decision points in the Management of Substance Use Disorder and provides clear and comprehensive evidence based recommendations incorporating current information and practices for practitioners throughout the DoD and VA Health Care systems. The guideline is intended to improve patient outcomes and local management of patients with substance use disorder. Disclaimer: This Clinical Practice Guideline is intended for use only as a tool to assist a clinician/healthcare professional and should not be used to replace clinical judgment. The guideline is formatted as two algorithms and 35 evidence-based recommendations: Module A - Screening and Treatment Module B - Stabilization and Withdrawal Questions about the SUD Guideline Synopsis of the 2022 SUDs CPG (2022) Telehealth for SUDs (2022) Retired CPG's can be found on our archive page A traditional goal of treatment for alcohol use disorder (AUD) is long-term cessation of alcohol use. Because this goal may not be achievable for many individuals, alternative goals can lead to substantial improvements in the health and lives of those with AUD. Such alternatives may include: Staying engaged in care, which can also facilitate prevention, diagnosis, and treatment of other conditions. Reducing high-risk behaviors (e.g., driving while intoxicated, alcohol-related unprotected sex). Improving quality of life and other social indicators, such as employment, stable housing, and risk of incarceration. Improving mental health. As with other chronic conditions, treatment goals for AUD should be individualized and are likely to change over time. It is important for healthcare providers and patients to discuss, agree on, and review AUD treatment goals regularly. If patients are unable to meet treatment goals, intensifying treatment with frequent visits, behavioral interventions, mental health assessment and treatment, and adjustment of dose or type of medication may be warranted. Currently, 3 medications are approved by the U.S. Food and Drug Administration (FDA) for the treatment of AUD: acamprostate, naltrexone, and disulfiram. Gabapentin and topiramate are additional evidence-based options for treatment. All of these medications are available in oral formulations, and naltrexone is also available in an extended-release (XR) formulation for intramuscular injection. Based on strong clinical evidence, acamprostate and oral or XR naltrexone are the preferred pharmacologic treatments for individuals with moderate-to-severe AUD who have a goal of reducing or abstaining from alcohol use [Jonas, et al. 2014; SAMHSA 2015]. In individuals with mild AUD, clinicians may consider pharmacologic treatment with oral acamprostate or oral or XR naltrexone. Clinical trials directly comparing acamprostate and naltrexone have not consistently established the superiority of one medication over the other in reducing heavy drinking. Individuals who use alcohol primarily for positive reinforcement (reward drinkers) may benefit more from naltrexone than those who drink for negative reinforcement, such as avoiding withdrawal (relief drinkers) [Mann, et al. 2018]. There is minimal and mixed evidence on whether combining naltrexone and acamprostate has an additive effect on alcohol consumption outcomes [Kiefer, et al. 2003; Anton, et al. 2006]. Acamprostate: Alcohol withdrawal produces a neurobiologic derangement in neuronal gamma-aminobutyric acid type A (GABA_A), N-methyl-D-aspartic acid (NMDA), and glutamate transmission, which can result in an excitotoxic state and neuronal injury. Acamprostate modulates transmissions from GABA_A and NMDA receptors, which can restore neuronal balance and mitigate the associated symptoms [Kalk and Lingford-Hughes 2014]. In clinical trials that have compared treatment with acamprostate and placebo, acamprostate increased the proportion of individuals who maintained complete abstinence from alcohol (complete abstinence rate), the mean cumulative abstinence duration, the percentage of alcohol-free days, and the median time to first drink [Paille, et al. 1995; Sass, et al. 1996; Whitworth, et al. 1996; Geerlings, et al. 1997; Pelc, et al. 1997; Poldrugo 1997; Tempsta, et al. 2000; Gual and Leheret 2001; Higuchi 2015; Plosker 2015]. A meta-analysis from 2014 found that acamprostate was significantly associated with decreased return to any drinking and with decreased percentage of drinking days throughout treatment [Jonas, et al. 2014]. Acamprostate should be initiated as soon as the individual has abstained from alcohol use (within 7 days) for the best treatment response. Acamprostate can be initiated if the individual is still actively using alcohol, but the efficacy of treatment during active alcohol use is unknown. Naltrexone: Naltrexone is an opioid receptor antagonist used in the treatment of individuals with AUD or opioid use disorder (OUD). Alcohol use increases the activity of the endogenous opioid system. As an opioid receptor antagonist, naltrexone interferes with the rewarding aspects of alcohol [Mason, et al. 2002; Pettinati, et al. 2006; Ray, et al. 2010]. Naltrexone may also decrease subjective cravings for alcohol [Maisei, et al. 2013]. A meta-analysis found no significant difference in alcohol consumption, a measure combining study-specific outcomes, between naltrexone and acamprostate treatment [Kiefer, et al. 2003; Anton, et al. 2006; Morley, et al. 2006; Mann, et al. 2013; Jonas, et al. 2014]. Clinical trials have shown that naltrexone improves alcohol use outcomes and, specifically, decreases the likelihood of return to drinking and the overall number of drinking days [Jonas, et al. 2014]. A meta-analysis of studies evaluating treatment with oral naltrexone showed that oral naltrexone 50 mg daily was associated with decreased return to any drinking and decreased return to heavy drinking, and XR naltrexone was associated with reduced heavy drinking days [Jonas, et al. 2014]. An ongoing randomized controlled trial by Lee, et al., is examining the effectiveness of oral versus XR naltrexone in producing abstinence or moderate drinking [Malone, et al. 2019]. Studies have shown that naltrexone is more effective in reducing alcohol consumption in individuals who use nicotine or cigarettes compared with those who do not [Fucito, et al. 2012; Anton, et al. 2018], which may be one factor in selecting pharmacologic treatment. Active alcohol use is not a contraindication to initiating treatment with naltrexone (oral and XR formulations); however, individuals should be monitored for alcohol withdrawal syndrome if alcohol use is significantly reduced abruptly. Disulfiram: Disulfiram inhibits the enzyme aldehyde dehydrogenase, which breaks down acetaldehyde, an alcohol byproduct. Consuming alcohol while taking disulfiram results in an accumulation of acetaldehyde and adverse reactions such as low blood pressure, tachycardia, facial flushing, nausea, vomiting, dyspnea, sweating, dizziness, blurred vision, and confusion. This adverse reaction is called the disulfiram-ethanol reaction [Bell and Smith 1949]. The psychological threat of these unpleasant physiologic effects is believed to be the primary mechanism for dissuading alcohol use in individuals with AUD [Skinner, et al. 2014]. Evidence is mixed on the effectiveness of disulfiram for the treatment of AUD. Well-controlled clinical trials do not support an association between disulfiram use and improvement in alcohol consumption outcomes [Jonas, et al. 2014]. However, it may be difficult to evaluate disulfiram in a double-blind study design because the threat of the physiologic effects of combining alcohol and disulfiram, which is present for both treatment and control groups, is directly related to the efficacy of the drug [Skinner, et al. 2014]. A meta-analysis showed that disulfiram was effective at improving consumption outcomes in open-label trials (no blinding for participants or researchers) but not effective in blinded randomized controlled trials [Skinner, et al. 2014]. Since the 1970s, studies examining the effectiveness of disulfiram have typically compared unsupervised administration of disulfiram with administration supervised by health professionals or by suitable delegated associates of the participant. Results suggest that disulfiram can be an effective treatment with supervised administration, but adherence is low with unsupervised administration [Fuller, et al. 1986; Jorgensen, et al. 2011; Skinner, et al. 2014; Brewer, et al. 2017]. Active alcohol use is a contraindication to disulfiram. At least 12 hours of abstinence from alcohol is required before initiating treatment with disulfiram to avoid an adverse reaction. Individuals should be warned that reactions may occur if alcohol is consumed up to 14 days after taking disulfiram. Gabapentin: The mechanism of action of gabapentin in treating AUD is not fully understood. However, evidence suggests that gabapentin modulates and stabilizes central stress systems that are dysregulated by the cessation of alcohol use [Roberto, et al. 2008; Roberto, et al. 2010]. Although gabapentin is not approved by the FDA for treatment of AUD, use of this medication has been associated with reductions in alcohol use and craving [Mason, et al. 2014; Mason, et al. 2018]. In addition, as an adjunct to benzodiazepines, gabapentin is effective in treating common symptoms of acute and protracted alcohol withdrawal, including anxiety and sleep disturbances [Karam-Hage and Brower 2000; Bazil, et al. 2005; Brower, et al. 2008; Myrick, et al. 2009; Lavigne, et al. 2012; Rosenber, et al. 2014; Mason, et al. 2018]. Active alcohol use is not a contraindication to initiating gabapentin [Myrick, et al. 2007]. Topiramate: The mechanism of action of topiramate in treating AUD is not fully understood. However, evidence suggests that topiramate enhances GABAergic neurotransmission and suppresses glutamatergic neurotransmission, helping to normalize and restore balance in the reward circuits of the brain [Shank and Maryanoff 2008; Frye, et al. 2016; Cheng, et al. 2018]. Like gabapentin, topiramate is not approved by the FDA for treatment of AUD, but it has been associated with fewer drinking days, fewer drinks per drinking day, decreased percentage of heavy drinking days, and increased number of abstinent days [Manhara, et al. 2019]. To a lesser degree, topiramate has been associated for treatment of AUD. Variables in studies of psychologically based interventions for alcohol use make it difficult to compare and interpret the evidence and extrapolate it to "real-world" settings and individual patients. These variables include type of approach, duration and number of sessions, type and training of the healthcare provider delivering the intervention, treatment setting, mode of delivery (in person or computerized), individual or group setting, risk level of alcohol use or AUD, and concurrent pharmacologic treatment. Most clinical trials examining pharmacologic treatment include a psychological component (e.g., MI or CBT for all treatment groups). MI is a way of helping patients recognize their current or potential problems and take action toward resolving them. The overall goal of MI is to increase the patient's intrinsic motivation to facilitate change from within, and the method is particularly useful for patients who are ambivalent about changing behavior or who are reluctant to change [Miller 2002]. This technique emphasizes the autonomy of the patient while providing a safe space for collaboration and consistent engagement to enhance the patient's motivation for change. The MI approach also helps the clinician identify the patient's readiness to change behavior and to use the patient's level of readiness as a starting point for counseling or treatment. It is worthwhile for healthcare providers to understand and use an MI-style approach when discussing alcohol use and AUD treatment plans with patients and to be aware of clinician and patient resources (see Online Resources: Psychologically Based Treatment for AUD, below). The key principles of MI are: Express empathy/avoid arguing. Develop discrepancy. Roll with resistance. Support self-efficacy (patient's belief they can successfully make a change). MET, adapted from MI principles, is a manual-based intervention designed to help patients explore ambivalence about alcohol use and develop intrinsic motivation to reduce or abstain from alcohol use [Lenz, et al. 2016]. CBT, individually or in groups, focuses on how thoughts, feelings, and behaviors influence each other and can be particularly useful for helping patients recognize and manage individual triggers for alcohol use. For CBT in an online format, see Computer Based Training for Cognitive Behavioral Therapy (CBT4CBT). Other psychologically based approaches include mindfulness and contingency management. A mindfulness approach seeks to help individuals with SUDs, including AUD, monitor for and relate differently to internal and environmental cues that trigger substance use [Bowen, et al. 2014]. Mindfulness-based relapse prevention programs have been associated with significant improvements in some alcohol-related outcomes compared with other psychosocial interventions, but data are limited [Bowen, et al. 2014; Grant, et al. 2017]. Contingency management aims to improve SUD treatment outcomes, such as engagement in care or abstinence, by providing incentives to patients. Studies have shown that contingency management was associated with significant improvements in alcohol-related outcomes, but the approach is not feasible in most medical settings [Prendergast, et al. 2006; Benishek, et al. 2014; Dougherty, et al. 2014; Barnett, et al. 2017; McDonnell, et al. 2019]. Mutual support programs: Self-Management and Recovery Training (SMART Recovery) focuses on self-empowerment and provides mutual support through in-person group meetings and online formats. The program uses rational emotive behavior therapy, a form of CBT, to facilitate changes in thinking and thus in emotions and behaviors [Horvath and Yeterian 2012]. Some studies have shown positive alcohol-related treatment outcomes, but data

are inconsistent [Beck, et al. 2017]. Some patients may find benefit in and connection to Alcoholics Anonymous (AA), a 12-step, mutual-support group approach based on fellowship and the role of a higher power. A recent systematic review identified high-quality evidence indicating that AA and 12-step facilitation interventions were at least as effective in increasing abstinence and improving alcohol-related outcomes as clinical psychological interventions (e.g., MET, CBT, other 12-step program variants) [Kelly, et al. 2020]. In some AA programs, however, participants who take pharmacologic medication for AUD can be made to feel unwelcome. Clinicians should collaborate with patients to set specific treatment goals about patient alcohol use and should document the treatment plan they agree on in the medical record [Dunn and Strain 2013; APA 2018]. Individual goals in the treatment plan may include, but are not limited to, abstinence, reduction in alcohol use, or avoiding alcohol consumption in high-risk situations (e.g., at work, before driving, when caring for children) (see the NYSDOH guideline Harm Reduction Approach to Treatment of All Substance Use Disorders). If pharmacologic treatment is initiated, clinicians should schedule frequent follow-up visits to provide patients with support and encouragement and to monitor treatment response, possible adverse effects, medication adherence, and signs of continued use or return to use. If a patient continues to use alcohol, pharmacologic treatment options, except for disulfiram, can be continued. However, clinicians should discuss treatment goals and possible modifications to the treatment plan with the patient. Adherence is essential for pharmacologic treatments to be effective, making pill burden an important practical consideration for clinicians. Treatment with acamprosate requires patients to take 2 pills thrice daily, and treatment with naltrexone requires patients to take 1 pill once daily. The choice of psychologically based treatment for AUD is based on patient experience and preference, social factors, treatment availability, and insurance, among other individual factors.

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