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Alcohol Use Disorder: Current and Emerging Therapies

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ABSTRACT

Alcohol use disorder (AUD) is a medical condition characterized by problematic and unhealthy patterns of alcohol use ranging from frequent to heavy alcohol consumption. It is a well-recognized psychiatric syndrome that includes a broad spectrum of symptoms and behaviors associated with alcohol misuse. People with AUD don't stop drinking alcohol despite emotional distress, social, occupational, or health problems. Pharmacological management of AUD depends on the patient's condition to reduce the symptoms and improve the patient's health. The US FDA approved three medications, namely naltrexone, acamprosate, and disulfiram for the treatment of AUD. Apart from these medications, psychological therapy, cognitive behavioral therapy, and encouraging patient participation in support groups have been showing promising results. The present review briefly discusses the epidemiology, symptoms, stages, diagnosis, screening, and emerging psychosocial therapies and pharmacotherapy of AUD including approved and off-label uses of drugs and newer agents.

Keywords: Alcohol use disorder, Acamprosate, Baclofen, Disulfiram, Gabapentin, Naltrexone, Nalmefene

INTRODUCTION

Human consumption of alcohol (ethyl alcohol, ethanol) has an evolutionary perspective of alcohol abuse that was evidenced first in hominoid ancestors, who consumed ripened fruits and fermented alcoholic products way back about 24 million years ago in human history and is conceived to have adaptive evolutionary significance.[1] In modern life, alcohol is one of the most widely consumed psychoactive drugs (substance use) and about 2.3 billion adults consume alcohol at least annually worldwide.[2,3] Acute alcohol consumption can lead to injury from aggression, accidents, and violence and often may lead to death at higher doses whereas long-term regular alcohol consumption results in alcoholism and alcohol abuse disorders.[3] Alcohol use disorder (AUD) is one of the most prevalent substance use disorders following tobacco worldwide.[3,4] It is a chronic psychiatric syndrome characterized by uncontrolled, problematic, and unhealthy patterns of alcohol consumption and preoccupation with alcohol that result in drinking frequent and/or heavy alcohol.[5]

1. Prevalence

Globally, lifetime alcohol use is most common in high-income countries as reported by more than 80% of adults whereas more variable rates have been reported in low-income and middle-income countries. Intriguingly, a majority of adults

in Europe (59.9%), the Americas (54.1%), and the Western Pacific (53.8%) reported at least annual alcohol consumption. According to the WHO data, an average of 6.4 l of pure alcohol was consumed by those above 15 years of age and older per year, which is 13.9 grams of pure alcohol per day.[3] It is estimated that 28.8 million adults ages 18 and older (11.2% in this age group) and 753,000 adolescents ages 12 to 17 (2.9% of this age group) had AUD in 2021.[6] In India, a prevalence of 1.2% of women and 29.2% of men consume alcohol.[7] The WHO World Mental Health Survey reported the percent prevalence of AUD in low-lower-middle-income countries (Ukraine, 43.3; China, 31.1), upper-middle-income countries (South Africa, 41.3; Brazil, 31.8), and high-income countries (Australia, 18; Israel, 26.5; US, 23.9) were 34.1, 32.5, and 21.4, respectively.[8]

2. Burden of AUD on Personal and Public Health

Alcohol is used as a self-medication to relieve psychological distress and side effects of medications that are used to treat psychiatric symptoms and disorders.[9,10] People with AUD have an impaired ability to control or stop alcohol use, which typically includes craving and manifestations of tolerance and/or withdrawal along with adverse psychosocial consequences, such as adverse social, occupational, and health consequences, emotional distress, or physical harm to themselves or others.[11] Additionally, alcoholism is the inability to control drinking due to both a physical and emotional dependence on alcohol. The 4th edition of the Diagnostic and Statistical Manual of Mental Disorders (DSM-4) guidelines includes two disorders, namely alcohol abuse and alcohol dependence. However, the DSM-5 guidelines combined these two DSM-4 disorders into a single disorder named AUD which is categorized into mild, moderate, and severe.[2,12] The 11th revision of the International Classification of Diseases (ICD-11) has mentioned two diagnoses for alcohol use with escalating severity (i.e., a harmful pattern of use of alcohol followed by alcohol dependence) and also a subclinical designation of hazardous alcohol use that denotes a risk factor that has not reached the point of having caused harms to the person or others.[2]

Excess alcohol consumption has been associated with more than 200 diseases and injuries.[13] The growing body of evidence shows that the amount of alcohol consumption has a causal relationship with several undesired health outcomes, such as immunodeficiency diseases (opportunistic infections), cancers (hepatocellular carcinoma), cardiovascular diseases (hypertension, atherosclerosis, myocardial ischemia, arrhythmias), metabolic disorders (diabetes, obesity, eating disorders, anemias), liver disorders (hepatitis, alcoholic fatty liver), and renal disorders (chronic kidney disease), respiratory infections (pneumonia, tuberculosis), bone damages (osteoporosis), perinatal complications (miscarriage, termination of pregnancy, stillborn, birth defects), mental disorders (psychosis, depression, anxiety, confusion), and neurological consequences (cerebral stroke, headaches, memory loss, neuropathic pain).[2,3,14,15] Prospectively, the World Health Organization (WHO) has developed several programs to meet the sustainable development goals (SDGs), also known as the Global Goals, adopted by the United Nations to reduce economic burden and to improve public health.[3]

3. International Standard Drink Definitions and Alcohol Limits

The definition of a standard drink alcoholic beverage varies widely across the world, from 8 g of alcohol in Iceland and the United Kingdom to 20 g in Austria. To estimate the prevalence of high-risk drinking globally, the WHO uses a measure called heavy episodic drinking, defined as consuming 60 g of alcohol or more on at least one occasion in the past 30 days. A standard drink of alcoholic beverage in the

US equals 14 g and heavy episodic drinking would be 4.25 standard drinks. In Australia, China, France, Ireland, and Spain, a standard drink equals 10 g, wherein exactly 6 standard drinks on a single occasion would constitute heavy episodic drinking.[16] In Australia, a standard drink of alcoholic beverage contains 10 g of pure alcohol. Importantly, the type of alcohol and alcoholic beverage makes no difference revealing the fact that 10 g of alcohol is 10 g of alcohol, whether it is in any type of beer, wine, or spirits (Table 1). Notably, the alcohol content in a standard drink definition would not change whether it is mixed with a soft drink, fruit juice, water, or ice.[17] More than 4 drinks per day or more than 14 drinks per week leads to alcohol abuse in men and more than 3 drinks per day or more than 7 drinks per week causes alcohol abuse in women.[18]

Table 1. Standard drinks of alcoholic beverages [17,18]

Beverage	% alcohol per volume	Volume size of drink (ml)
Light beer	2.7	425
Mild strength beer	3.5	375
Full strength beer	4.9	285
Regular cider	4.9	285
Sparkling wine	13	100
Wine	13	100
Fortified wine (sherry, port)	20	60
Spirits (vodka, gin, rum, whiskey)	40	30

3.1. Moderate alcohol consumption: According to the Dietary Guidelines for Americans, which are intended to help individuals improve and maintain overall health and reduce chronic disease risk, moderate drinking is defined as up to 1 drink per day for women and up to 2 drinks per day for men.[19,20]

3.2. Low-risk drinking and alcohol use disorder (AUD): A low-risk drinking is defined as no more than 3 drinks on any single day and no more than 7 drinks per week for women whereas no more than 4 drinks on any single day and no more than 14 drinks per week for men. Certainly, about 2 in 100 people who drink within these limits meet the criteria for AUD. However, even within these limits of alcohol drinking is associated with risk if one drinks too quickly or if one has co-morbid conditions.[18]

3.3. Binge drinking: Binge drinking is defined as a pattern of alcohol drinking wherein blood alcohol concentration rises to 0.08 g per deciliter (0.08%) or more. This generally happens when a woman consumes 4 standard drinks or a man consumes 5 standard drinks in a 2-hour time frame or one occasion on at least 1 day in the past 30 days.[18-21]

3.4. Extreme binge drinking: It is also known as high-intensity drinking, which denotes alcohol drinking at levels crossing the binge drinking threshold, resulting in extremely elevated blood alcohol concentration. Invariably, it is defined as 2 or more times the gender-specific binge drinking thresholds (i.e., 10 or more standard drinks for men, and 8 or more for women).[16,18]

3.5. Heavy drinking: Heavy drinking is defined as binge alcohol drinking on each of 5 or more days in the past 30 days.[18,21]

4. Blood Alcohol Levels and Their Physiological Effects

Acute alcohol consumption results in a blood alcohol level 0.08 g% (8 mg/dl), which is considered as the normal range. A blood alcohol level of 10-40 mg/dl causes mild euphoria and relaxation whereas 50-70 mg/dl (0.05-0.07%) of blood alcohol causes motor impairment. In Germany, a blood alcohol concentration of 5 mg/dl (0.05 g%) is the legal limit for driving, however, 80 mg/dl (0.08 g%) is the legal limit of driving in the US as it causes impairment of driving skills. Notably, emotional swings and depression are observed in individuals whose blood alcohol limit is 80-120 mg/dl.

Considerably, motor function, physical and mental balance, speech, thought process, judgment, and vision are severely affected at 120-200 mg/dl of blood alcohol level. The person may experience nausea, vomiting, irritation, agitation, delirium, anxiety, diaphoresis, visual hallucinations, tremors, seizures, headache, tachycardia, temperature elevation, incontinence, alcohol intoxication, stupor, blackout, and total loss of consciousness when exceeding levels of alcohol at 200-400 mg/dl present in blood and that may lead to coma and death when blood alcohol level exceeds 400 mg/dl.[2,22,23]

5. Symptoms

Health care professionals use DSM-5 criteria to assess the severity of the disorder based on the number of criteria a person meets based on their symptoms viz., mild (2-3 criteria), moderate (4-5 criteria), and severe (6 or more criteria).[11] Healthcare providers look for the following signs and symptoms, such as (a) blacking out (not remembering things that happened), (b) continuing to drink even if it causes distress or harm to the person or others, (c) drinking more or longer than planned, (d) feeling irritable or cranky when not drinking, (e) frequent hangovers, (f) getting into dangerous situations when drinking (for example, driving, having unsafe sex or falling), (g) giving up activities and preoccupation with alcohol drinking, (h) having cravings for alcohol, (i) having repeated problems with work, school, relationships or the law because of drinking, (j) needing to drink more and more to get the same behavioral and psychological effect, (k) not being able to stop drinking once started, (l) spending a lot of time drinking or recovering from drinking, (m) wanting to cut back but not being able to, (n) obsessing over alcohol.[24,25] In the early stages, patients may be asymptomatic or present with hypertension or insomnia whereas nausea, vomiting, hematemesis, abdominal distension, epigastric pain, weight loss, jaundice, or other signs of liver dysfunction are reported in the later stages. Other warning signs and symptoms include aggressive behaviors, violence, decreased resistance to infections, dementia, instability, visual impairments, seizures, tremors, confusion, tingling sensation, risk of ulcer, risk of accidents while drunk and driving, heart failure, blood clotting disorders, unwanted falls, sexual dysfunction in men, malnutrition, vomiting and diarrhea, neuropathy, in women-giving birth to deformed babies or low birth weight babies.[25]

6. Risk Factors

Risk factors for developing AUD depend upon how much, how quickly, and how often a person drinks alcohol. AUD is 50% heritable and 50% environment-related.[2,9] Alcohol misuse (binge drinking, heavy alcohol use) over time increases the risk of AUD. Other factors for developing AUD include genetic factors, family history of alcoholism, drinking from childhood, steady drinking over time, history of trauma, having bariatric surgery, social and cultural factors, psychiatric conditions like depression, post-traumatic stress disorder, childhood trauma, mental health conditions, and chronic health conditions.[2,9,11,26]

7. Stages of Alcohol Use Disorder [24,27-29]

Alcohol use that turns into a use disorder develops in stages. According to Jellinek, people addicted to alcohol tend to pass through four progressive sequences, phases, or stages. These include (1) the "pre-alcoholism" phase, (2) the "prodromal" phase, (3) the "crucial" stage, and finally, (4) the "chronic" phase, followed by (5) the recovery phase (Four references).

7.1. Stage one – Pre-alcoholic or At-risk stage (binge drinking/social drinking): This is when the person drinks socially, to relieve psychological stress, emotions, and tension, escape challenges, or feel better. This is sometimes referred to as "early relief drinking." At this stage, a person may not experience or perceive any damaging effects of their drinking but drinks more and more

frequently than before to experience the same pleasant effects. This causes progressive physiological changes in the individual to start developing a tolerance for alcohol.

7.2. Stage two – Prodromal or Early alcohol use disorder (alcohol abuse): In this stage, troubling physical signs and symptoms emerge as the levels of alcohol consumption increase and even gulps the first couple of drinks. The person drinks alone or in secret and is abnormally preoccupied with drinking and progresses to memory lapses and recurrent blackouts that may accompany binge drinking episodes. At this point, the individual develops an increase in alcohol tolerance, regular severe hangovers, and insomnia that affects emotional well-being, such as low self-esteem, increased irritability, increased spending on alcohol, and growing feelings of guilt or shame about their behavior.

7.3. Stage three – Mid-stage alcohol use disorder (crucial phase, quite a serious problem drinking): A person loses control on alcohol use, makes excuses, or blames others. The person may stop drinking entirely or alter their pattern of drinking but usually repeatedly fails, develops dominant negative emotions, potential suicidal ideation, hopelessness, mood swings, irritability, and visible signs of intoxication, begins physical dependency on alcohol, begins drinking in the morning, has poor nutrition, significant liver damage, such as alcoholic hepatitis, fatty liver disease, liver fibrosis, and liver cirrhosis, and causes problems with daily life (work, family, financial, physical and mental health).

7.4. Stage four – End-stage alcohol use disorder (chronic phase, late alcoholic): A person's daily life involves binge drinking for a prolonged time to the exclusion of food, intimacy, health, and happiness., physical and mental decline continues, and experiences impaired thinking or psychotic episodes. Their tolerance for alcohol declines, don't experience psychological relief from drinking, develop high levels of physical alcohol dependence, and even small amounts of alcohol cause marked inebriation. Indeed, stopping drinking at this point would result in severe and life-threatening withdrawal symptoms. The person develops hallucinations, paranoia, depression, and anxiety disorders. At this end stage, vital organs' function compromise, including cirrhosis of the liver, brain damage leading to cognitive impairments, increased risk of cancer, and death are now close.

7.5. Stage five – Recovery phase (rehabilitation). According to the Jellinek Curve, the first step of recovery starts with an "honest desire for help." The affected person believes that there is no real chance of recovery or that it would be too painful to attempt. In reality, severe alcoholism is still treatable. Though the end-stage AUD is a severe medical condition, however, seeking help can often reverse or at least prevent vital organ function, and physical, emotional, and mental balance from becoming worse. Early in the rehabilitation process, a person will learn and motivate that addiction is a treatable disease and it is never too late to seek help no matter how long an alcoholic has been struggling. At this point, the affected person will perform an honest self-assessment of their life and of their character.

8. Diagnostic Tests

Urine and blood tests are reliable tests for the actual use of alcohol. Blood alcohol content (BAC) is the common test used; however, these do not differentiate people with AUD from people without. Other tests that are commonly used in diagnosis are macrocytosis (enlarged mean cell volume), elevated gamma-glutamyl transferase (GGT), aspartate transaminase (AST), alanine transaminase (ALT), an AST to ALT ratio of 2:1 or more, and high carbohydrate-deficient transferrin (CDT). Importantly, BAC is a useful test to diagnose alcohol tolerance, which is a sign of alcoholism.[30,31] Apart from these abnormalities, electrolyte and acid-base abnormalities including hyponatremia,

hypokalemia, hypomagnesemia, hyperammonemia, hyperuricemia, anemia, thrombocytopenia, coagulopathy, decreased vitamin B12 and folate levels, metabolic acidosis, and respiratory alkalosis are common in people with AUDs.[30,32]

Inarguably, single traditional tests rarely differentiate alcoholic liver disease from non-alcoholic liver disease as GGT and CDT increase in both diseases. Indeed, alcohol abuse is present in 20–90% of liver diseases and 50% of cirrhosis. Moreover, CDT is more specific than GGT in alcohol abuse. Notably, the De Rittis Index (AST/ALT) is the most important and effective biomarker in differentiating alcohol from non-alcoholic liver injury. The index value >1.5 is suggestive and a value >2 is almost a confirmation of the alcoholic etiology of a liver injury.[30-32]

Recent advances in laboratory investigation embraced a series of new biomarkers of alcohol abuse and AUD. Ethyl glucuronide (EtG) and ethyl sulfate (EtS) are the best indicators of current alcohol intake of a longer recognition duration. Although alcohol is eliminated from the blood in about 8 h, in particular, EtG exists in blood for about 36 h and in urine for 3-5 days after binge alcohol intake, and EtS is detectable in urine bot 16-27 h. An increase in sensitivity levels of β-hexosaminidase (β-HEX) activity in serum and urine, a reduction in plasma sialic acid index of apolipoprotein J (SIJ) in alcoholics with a specificity of ~100% wherein the levels become normal after several weeks of abstinence from alcohol (T½ = 4–5 weeks), an increase in total serum sialic acid (TSA) in saliva, urine, and serum, and elevated fatty acid ethyl esters (FAEEs) in blood are some of the widely used biomarkers.[31,32]

9. Screening

It has been well established that blood and urine tests for biological markers are not as sensitive as screening questionnaires. Importantly, screening is recommended in all age groups, particularly, among those over the age of 18 years. These screening tools are mostly self-reports in questionnaire form and are used to detect a loss of control of alcohol use.[2,33] Indeed, healthcare professionals employ one of several valid screening tools, such as the CAGE questionnaire, which is an initial screening test to identify persons with early-warning symptoms and AUDs. The CAGE questionnaire comprises 4 questions, viz., (1) Have you ever felt the need to **C**ut down on your drinking?, (2) Have you ever been **A**nnoyed by people criticizing your drinking?, (3) Have you ever felt **G**uilty about your alcohol consumption?, and (4) Have you ever felt the need for an **E**ye-opener to steady your nerves or get rid of a hangover? A score of 2 or more on the CAGE questionnaire indicates the need for further evaluation and diagnosis of AUDs.[2,24,33]

The Paddington Alcohol Test (PAT) is used to screen for alcohol-associated problems by the Accident and Emergency departments. The Alcohol Dependence Data Questionnaire (ADDQ) is a more sensitive diagnostic test than the CAGE questionnaire for the detection of alcohol dependence. The Michigan Alcohol Screening Test (MAST) is a screening tool for alcoholism widely used by courts to determine the appropriate sentencing for people convicted of alcohol-related offenses. The Alcohol Use Disorders Identification Test (AUDIT), a screening questionnaire developed by the WHO, is a highly validated screening tool worldwide.[25,34] In the AUDIT scoring system, a score >8 indicates the presence of AUD. A three-question shorter version of AUDIT is AUDIT-C and a score $\geq$ 3 for women and $\geq$4 for men indicates the presence of AUD.[35,36] Patient information regarding past medications, past medical history, the quantity of alcohol consumed, frequency of drinking, and type of alcohol consumed taken from the patient's family member or caretaker is important in diagnosing.[35] The US Preventive Services Task Force recommends the 10-Question AUDIT (AUDs Identification Test), the 3-Question AUDIT (AUDIT-C), and the

Single-Question Screening Test (SQST) for screening of AUDs.[2,33-35]

10. Therapeutic Approaches of AUD

The goals of therapy of AUD are (i) to limit alcohol consumption, (ii) to manage alcohol withdrawal symptoms, and (iii) to encourage abstinence using pharmacological and non-pharmacological approaches.[5,36-40] It has been reported that no standard drinks per week or zero level of alcohol consumption has been shown to minimize harmful health outcomes indicating the recommended safe level of alcohol consumption is zero.[4,38,40] To reduce the health risks associated with drinking alcohol, healthy adults drink should not more than 10 standard drinks a week and not more than 4 standard drinks a day. People under 18 or the minimum legal age for drinking and children should not drink alcohol. Women of childbearing age, women who are expecting pregnancy, pregnant, nursing, or breastfeeding should not drink alcohol to prevent harm from alcohol to the unborn child or newborn baby.[17,18,39] Further, people who have a medical condition that alcohol can aggravate, individuals taking certain over-the-counter (OTC) or prescription medications that interact with alcohol, people driving vehicles or operating machinery, those who plan to do work shortly after drinking, or participate in activities that require skill, coordination, and alertness should avoid drinking completely. Importantly, people should avoid alcohol drinking while recovering from AUD or when unable to control the amount that they drink.[5,17,18,39,41] Although various approaches have been evaluated for the management of AUDs and their complications, evidence-based, highly validated, and well-accepted psychosocial therapies, pharmacotherapy, and alternative systems of medicine remain a mainstay in clinical practice.

10.1. Psychosocial therapies

10.1.1. The current psychosocial treatments in clinical practice are i) rehabilitation programs, ii) behavioral treatments, iii) cognitive-behavioral therapy (CBT), iv) learning new skills, v) problem-solving skills, vi) motivational enhancement therapy, vii) motivational interviewing,[42] viii) community-based therapeutic education program,[43] ix) community-based drinking reduction program,[44] x) therapeutic community-oriented program,[45] xi) group music therapy,[46] xii) behavioral couples therapy, xiii) cue exposure therapy, xiv) brief interventions, including computerized, web-based, and mobile interventions, xv) community reinforcement, xvi) contingency management, xvii) marital and family counseling, xviii) psychological counseling, xix) out-patient counseling, xx) self-help groups, and xxi) mutual-support groups.[5,38,46,47]

Behavioral treatments are focused on changing alcohol-drinking behavior and self-motivational practice through counseling. These modalities are guided by health professionals and such practice methods have been beneficial and supported by evidence-based studies.[47] Cognitive-behavioral therapy employs a wide range of social learning theories and stress-coping skills. From the perspective of CBT, AUDs including alcohol dependence are a learned behavior that can be improved and modified by several learning cognitive and behavioral techniques. In general, cognitive behavioral therapists focus on promoting awareness and increasing motivation to quit or reduce alcohol consumption, helping patients to identify highly risk situations for drinking alcohol, helping them to understand the socioeconomic, family, and personal attributes in life, and realizing the facts of undesired consequences of overusing alcohol, improving self-esteem, discuss the idea of controlling dysfunctional drinking to prevent relapse, and improve social skills, anxiety, and stress management.[42,47,48] Psychological counseling and therapy for groups and individuals help to better

understand AUD and associated complications and risk of socioeconomic disturbances and cancer, and support recovery from the psychological aspects of alcohol use.[37,38]

Alcoholics Anonymous (AA) is the most commonly practiced and widely accepted self-help group. It is the choice of patients to find an AA group they feel comfortable in. The AA is a 12-step program which is the most common self-help group for overcoming alcoholism. The stage of recovery from alcoholism embraces the purpose of life with an inner reflection by confronting failures and shortcomings to break out of old and unhealthy patterns of alcoholism. In general, AA provides patients with nondrinking friends who are always available and a nondrinking environment in which to socialize and stay in comfort. Patients share common goals, read motivation books, and also hear others discuss every rationalization for their own and others' drinking habits. The help they give other patients with AUDs may provide them with the self-regard and confidence formerly found only in alcohol.[39,49]

Many patients with AUDs are reluctant to go to AA and find individual counseling or group or family treatment more acceptable. Alternative organizations, such as LifeRing Secular Recovery (Secular Organizations for Sobriety), Women for Sobriety, Al-Anon and Alateen, Celebrate Recovery (Christian focus), Rational Recovery (non-spiritual), Recovery Dharma (mindfulness, Buddhist focus), and Self-Management and Recovery Training (SMART) Recovery exist for patients seeking another approach.[24,38,47,50]

10.1.2. Emerging psychosocial therapies have been gaining importance owing to their ease of adaptability, acceptance, and beneficial outcomes in in patients with AUDs. "SWiPE," a gamified, personalized alcohol ApBM smartphone app based on Approach bias modification (ApBM). ApBM is a computerized cognitive intervention that trains people to "avoid" alcohol-related images, to "approach" nonalcohol images, and that reduces the likelihood of relapse when administered during residential alcohol treatment.[51] It also includes telephone and smartphone-based remote continuing care interventions.[52] Fit&Sober app is developed to facilitate self-monitoring of physical activity engagement, daily mood, alcohol cravings, increase awareness, and also serve as a resource for alcohol relapse prevention strategies.[53] Further, Drinks: Ration Mobile App uses a mobile alcohol reduction intervention that is personalized and developed to reduce alcohol consumption[54] whereas HealthCall Smartphone Intervention reduces heavy alcohol drinking in adults with HIV[55] In addition to this, SoberDiary is an integrated system that includes a smartphone application, a portable Bluetooth breathalyzer, and a back-ended server support system. It is used to build a continuous care system based on smartphone technologies to support relapse prevention of AD after detoxification,[56] Echo app v2.0 is a virtual agent-assisted intelligent rehabilitation treatment that involves a "psychological-cognitive-physiological" multidimensional assessment and rehabilitation management system. This system consists of the user side, administer side, and server side. The user side consists of an assessment module and an intervention module. The administrator side is used to manage patient accounts, and access and download assessment and intervention data. The server side connects the administrator side and the user side to obtain and integrate data on both sides. Importantly, the assessment module, connected to the administrator and server, is used to evaluate the severity of substance use disorders, psychological and emotional state, and various physiological indicators. The intervention module, which is connected assessment module, administrator, and server sides, can interact with participants through a virtual digital image of a therapist.[57]

Recent advances in neuromodulation techniques have prompted to evaluation of promising beneficial effects and their potential for the development of novel treatments for AUDs. Several neuromodulatory approaches, such as deep brain stimulation, transcranial magnetic stimulation (TMS**)**, transcranial electrical stimulation (TES), including transcranial direct current stimulation and transcranial alternating current stimulation, and real-time neurofeedback have already been evaluated in patients with AUD and are still undergoing further investigation.[50,58]

10.2. Alternative medicine: Owing to their wider acceptability and success rate, several alternative systems of medicine are routinely recommended by medical professionals. Indeed, AUD-affected patients are avoiding and/or replacing conventional medical treatment or psychotherapy with alternative medicine. However, it has been well evidenced that alternative systems of medicine if used in addition to pharmacological treatment plans when recovering from AUDs, these techniques may be helpful. Yoga is a series of postures and controlled breathing exercises that may help relax and manage stress. During Spiritual practice and Meditation, the patient improves centralized focus and attention and gains self-control to eliminate the series of disturbed and mixed thoughts that may be crowding the mind and causing stress. Acupuncture involves the insertion of hair-thin needles under the skin and may help reduce anxiety and depression.[5,38]

10.3. Pharmacotherapy

Pharmacological therapy of AUD is effective in patients with moderate to severe disorders. However, these medications have shown beneficial and desired outcomes when prescribed in conjunction with psychosocial interventions. These agents are recommended after a thorough evaluation of a patient's drinking pattern and overall health, including major organ functions, such as liver and kidney that help design a treatment plan and assess the appropriateness of these medications for AUDs.[5,37-41,59,60]

10.3.1. FDA approved and therapeutic choices of drugs in AUD (naltrexone, acamprosate, disulfiram; Table 2)

a) Naltrexone:

It was an FDA-approved first-line agent for the treatment of AUD in 1994 and was first approved for the management of opioid dependence in 1984. Further, the FDA approved extended-release intramuscularly (IM) injectable naltrexone to treat people with alcohol dependence in 2006 and approved for the treatment of opioid use disorder in 2010.[35-37,50,60] It is also approved for use in several European countries and India. It is a nonselective antagonist that acts by blocking μ, δ, and κ-opioid receptors. It is well known that endogenous opioids (endorphin, enkephalin, dynorphin) are released following alcohol consumption, inhibit the release of dopamine, contribute to positive reinforcement effects, and promote continued drinking in the alcohol-dependents. It also alters the hypothalamic-pituitary-adrenal axis and reduces the rewarding effects of alcohol by modulating the dopaminergic mesolimbic pathway thereby decreasing alcohol consumption.[37,50,60,61] It has been shown that naltrexone reduces heavy drinking by reducing craving for alcohol, and decreases the relapse rate, and number of drinking days in most patients who take it consistently.[5,37,50] It can be given safely to the target population and pregnant who wish to reduce heavy drinking or pursue abstinence, do not have remarkable hepatic insufficiency or failure, and are not taking opioids.[60] It also helps in complete abstinence from alcohol. It is given 50 mg daily per oral and 380 mg for 4 weeks IM.[35,36,40,62] Both the oral and IM formulations are available with a black box warning for hepatotoxicity. Therefore, liver function tests (LFTs) should be monitored regularly. It is partially contraindicated in

individuals whose LFTs are three to four times the upper limit of normal and should be given with advice from the experts. It is contraindicated in people on opioid therapy, acute hepatitis, and hepatic failure.[37] At the usual daily dose of naltrexone (i.e., 50 mg), approximately 10% of patients experience anxiety, sedation, or nausea and hepatotoxicity has been reported at higher daily doses (i.e., 300 mg).[9] Common adverse effects of oral naltrexone include somnolence, nausea, vomiting, decreased appetite, abdominal pain, insomnia, and dizziness.[36,37] The severity of side effects can be reduced by taking this medication with food. Moreover, it is a nonselective opioid antagonist, blocks the analgesic effect of opioids, and can precipitate opioid withdrawal symptoms.[40,63] It should not be given 48 to 72 hours before surgery and in an emergency non-opioid analgesia is preferred to relieve pain.[62-64] The combination use of naltrexone and acamprosate had no additional beneficial effect in clinical trials[5,62] However, it has an advantage over disulfiram in that it can be taken even when a patient continues to consume alcohol. It is also used to promote abstinence in opioid use disorder rendering this medication an attractive choice for patients with comorbid alcohol and opioid use disorders.[37,41,61,62]

b) Acamprosate:

It was first approved in 1989 for the treatment of alcohol dependence in Europe and then approved for use in the US in 2004, followed by Canada and Japan.[5,37,4150] Acamprosate, a synthetic analog of gamma-aminobutyric acid (GABA), is an agonistic at $GABA_A$ receptors and a weak antagonistic at N-methyl-D-aspartate receptors and metabotropic glutamate receptor 5.[7,61,62] It is shown to reduce glutamate levels in the brain. It is recommended for patients who want continued sobriety after a period of abstinence and who do not have severe renal impairment. Indeed, improved therapeutic outcomes have been reported in those with an extended length of sobriety before treatment initiation, and demonstrated primary effectiveness for maintaining abstinence from alcohol. It has been shown to decrease the relapse rate and the number of drinking days in patients who relapse. Moreover, it is equally efficacious as naltrexone in reducing the return to heavy drinking, the percentage of drinking days, and the return to any drinking.[37,62,65] It is well tolerated and does not interact with other psychotropic drugs.[37] It is highly effective in those with negative emotional state-based cravings (relief drinkers) and has also been shown to reverse alcohol-associated changes in sleep patterns and help with sleep deprivation-induced cravings.[41,62,65] The FDA-approved daily dosage of the acamprosate is 333 mg and two 333 mg enteric-coated tablets are given three times per day (2 g orally/day). In patients with moderate renal impairment (creatinine clearance 30-50 ml per minute), initially one tablet three times per day is recommended.[65,66] It is a widely used and recommended alternative to naltrexone.[37,60] Side effects include diarrhea, dizziness, headache, insomnia, anxiety, depression, asthenia, anorexia, pain, flatulence, nausea, pruritus, dry mouth, paresthesia, and sweating.[66,67] Notably, it is not associated with any psychotropic effects. Renal function should be monitored at regular intervals as dose reduction is required for mild-to-moderate renal impairment. Acamprosate is not recommended for use in severe renal impairment (creatinine clearance less than 30 mL/min). It is contraindicated in patients with severe renal dysfunction.[68] Importantly, acamprosate is not affected by liver function and is safe for use in patients with liver disease in which naltrexone and disulfiram are contraindicated. It should be avoided in patients with hypercalcemia (total calcium > 10.3 mg/dL or ionized calcium > 5.4 mg/dL).[40,61,65]

c) Disulfiram:

It was approved in 1949 and has been in use in the treatment of AUD for more than 75 years.[9,36,41] It acts by inhibiting aldehyde

dehydrogenase-2 (ALDH) in the liver and the brain which converts acetaldehyde to acetate and causes accumulation of acetaldehyde in blood.[5,37,61,62] Such elevated acetaldehyde in the blood causes unpleasant effects, such as nausea, vomiting, headache, and flushing, which develop after alcohol consumption, and lead to negative reinforcement that in turn promotes alcohol avoidance in AUD. Disulfiram therapy is started after 48 h of total abstinence and duration of action up to 14 days after stopping.[60,62] Indeed, drinking alcohol within 12 h of taking disulfiram causes facial flushing in 5 to 15 minutes, then intense vasodilation of the face and neck with suffusion of the conjunctivae, throbbing headache, tachycardia, hyperpnea, and sweating. Moreover, nausea and vomiting may follow in 30 to 60 minutes with high doses of alcohol and may lead to hypotension, dizziness, and sometimes fainting and collapse. The reaction can last up to 3 h.[62,69] It is given 250 mg per day per oral and increased to 500 mg once per day. Side effects include skin flushing, tachycardia, hypotension, sweating, shortness of breath, nausea, vomiting, palpitations, headache, optic neuritis, peripheral neuritis, peripheral neuropathy, drowsiness, headache, allergic dermatitis, metallic or garlic-like aftertaste.[37,66] The efficacy of disulfiram is directly proportional to the motivation of the patient to take the medication, the drug-taking behavior of the patient, and improved medication adherence as there is a threat of aversive reaction taken with alcohol.[50,61,69] The greatest efficacy of the drug is observed with supervised use. The drug also acts by inhibiting the dopamine-beta-hydroxylase, so increasing dopamine levels, thereby it may reduce craving for both cocaine and alcohol. It may be given on an outpatient basis after 4 or 5 days of abstinence. The initial dosage is 0.5 g orally once/day for 1 to 3 weeks, followed by a maintenance dosage of 0.25 g once/day, and the therapeutic effects may persist for 3 to 7 days after the last dose. In addition, LFTs should be monitored at regular intervals for elevated transaminases. Of particular note, patient education, regular physician visits, patient counseling, and medication adherence are required to encourage the continuation of disulfiram as part of an abstinence program.[9,37,41,69] Owing to these monitoring requirements, it is now considered as a second-line agent in the management of AUDs. It is contraindicated during pregnancy, in patients with cardiac decompensation, in coronary artery disease, psychosis, and hypersensitivity to this medication and thiuram derivatives. Notably, pharmaceutical dosage forms that contain alcohol, hydroalcoholic preparations of phytopharmaceuticals, and culinary gastronomic preparations (eg, tinctures, elixirs, alcohol-containing mouthwash, cooking wine, certain vinegar preparations, kombucha, and certain OTC liquid cough and cold preparations, which contain as much as 40% alcohol) should also be avoided.[5,37,40,41,60,62]

10.3.2. Non-FDA approved drugs

Many approved drugs have been repurposed, several newer agents have been tested, and also undergoing clinical trials in patients with AUDs. Healthcare professionals have been repurposing and prescribing these approved drugs to the affected patients in their clinical practice for off-label use. These repurposed drugs are indicated for the management of AUDs in selected populations based on the acceptable results from the clinical trials and promising pragmatic approaches.[9,36,61] These repurposed drugs include adrenergic α-antagonists (doxazosin, prazosin), aripiprazole, baclofen, bupropion, gabapentin, gamma-hydroxybutyrate (GHB), ibudilast, kudzu (isoflavone), memantine, metadoxine, mifepristone, N-acetyl cysteine, nalmefene olanzapine, ondansetron, oxytocin, psilocybin, quetiapine, rimonabant (CB1 receptor antagonist), selective serotonin reuptake inhibitors (SSRIs; sertraline, fluoxetine), spironolactone (nonselective mineralocorticoid receptor (MR)

antagonist), suvorexant (dual orexin antagonist), topiramate, varenicline, and zonisamide (Table 2).[5,9,35-41,50,60,61,66,70,71]

a) Nalmefene: It acts as an antagonist at μ- and δ-opioid receptors and acts as a partial agonist at κ-opioid receptors. It is not currently approved in the US but was approved for AUD treatment in Europe in 2013. It is approved in the US for opioid overdose.[61] It is used to reduce alcohol consumption but not necessarily abstain in patients with alcohol dependence, including men who consume approximately more than four standard drinks per day of ethanol (more than 60 g) or women who consume approximately more than three standard drinks per day (more than 40 g).[36] When compared to placebo, it showed reduced relapse rates in AUD.[67] The side effects of nalmefene include nausea, dizziness, insomnia, headache, vomiting, fatigue, and somnolence).[36] However, its use is not associated with hepatotoxicity. Moreover, the approval and recommendations for its use in AUDs have been widely criticized as many of the efficacy trials had not defined the target population, reported unplanned subgroup analysis, used inappropriate comparison with placebo instead of standard approved drugs, and were limited by questionable relevance of alcohol consumption.[37,72,73]

b) Sodium oxybate: Gamma-hydroxybutyrate (GHB), a sedative agent, enhances inhibition at both $GABA_A$ and $GABA_B$ receptors and is used for the treatment of narcolepsy. In a few European countries, such as Italy, Austria, and France, a form of GHB, marketed as sodium oxybate, is approved for AUD only.[61] It acts as an alcohol substitute, a replacement therapy, reduces the craving for alcohol, and prevents alcohol withdrawal syndrome and allostasis. It is used for the alcohol withdrawal syndrome for a short term only (7-10 days) in hospitalized patients whereas it is not approved for the chronic treatment of AUDs for the prevention of relapses and the maintenance of abstinence.[61,73,74] This medication should be prescribed to severe alcohol-dependent patients with a very high drinking risk level associated with psychiatric comorbidities. In particular, this drug is not recommended for alcoholic patients affected by co-addiction to heroin or cocaine and/or psychiatric comorbidity, such as borderline personality disorders as it is associated with a high risk of developing a craving for and abuse. Therefore, prescribing this drug requires careful selection of patients who are likely to be adherent to dosing recommendations and also necessitates careful monitoring of its use.[73-75]

c) Metadoxine: It is approved in India, Russia, several European countries, and Brazil for treating acute alcohol intoxication. It facilitates the elimination of alcohol from blood and tissues when given as a single 900 mg intravenous dose. It has also been used to treat alcohol dependence based on its properties as a selective serotonin receptor subtype $5\text{-}HT_{2B}$ antagonist and a monoamine-independent GABA modulator.[72,76] It has been reported that patients had maintained abstinence for 3 months when given 1500 mg/day in divided doses.[76] Further, it has shown promising results in patients with severe alcoholic hepatitis survivors who received metadoxine in addition to standard therapy and maintained abstinence for 6 months. Although it is a safe drug, its use in AUD needs to be investigated in a larger population.[72,76,77]

d) Topiramate is an anticonvulsant medication but it is prescribed in treating AUD. Notably, it is more efficacious in treating AUD when compared with a placebo.[67,73] Topiramate therapy can also be considered as an effective adjunctive therapy in lower doses (75 mg daily) when combined with psychotherapy for alcohol dependence. It had shown a significant beneficial effect on heavy drinking and the number of drinks per drinking day but had a weak effect on the number of abstinent days.[78,79]

e) Gabapentin is a calcium channel or GABA neurotransmission modulator. It is

an FDA-approved drug used in epilepsy and neuropathic pain but it is used in second-line therapy in AUD, no dose adjustments are required in patients with hepatic impairment.[35,73,78]. Its daily dose of 600 mg found positive benefits in very heavy drinkers.[79]

f) Baclofen is a GABA-B receptor agonist and studies have shown that reduces alcohol consumption. It is approved for AUD in France.[61] In clinical trials conducted in Italy, the results showed that baclofen reduced alcohol consumption but trials conducted in the US reported that it was not effective in reducing alcohol consumption but decreased anxiety in patients with AUD.[78,79] (4). Baclofen 30 mg daily dose has shown more positive benefit compared to placebo in abstinence, craving, and daily alcohol intake. A higher dose (60 mg/day) produced a more robust response in the reduction of the number of drinks per day.[9,66,73]

Table 2: Therapeutic choices in the management of AUDs [5,9,35-41,50,60-62,72,73,78]

Drug	Dose	Side Effects	Precautions
FDA Approved Pharmacotherapy			
Naltrexone	Initial dose: 25 mg/day, Maintenance dose: 50 mg/day; Use for 6 months or longer	Nausea, vomiting, dizziness, abdominal pain, anorexia, headache, daytime, sleepiness, hepatotoxicity with high doses	Liver disease (Acute hepatitis, acute liver failure, chronic liver failure), Use of/likely use of opioids, Active opioid use, Analgesia in surgeries
Long-Acting Injectable Naltrexone	380 mg intramuscularly/month	Injection site reactions, nausea, vomiting, dizziness, abdominal pain, anorexia, headache, daytime, sleepiness, hepatotoxicity	Liver disease (Acute hepatitis, acute liver failure, chronic liver failure), Use of/likely use of opioids, Active opioid use, Analgesia in surgeries
Acamprosate	If >60 kg - 1998 mg/day (~ 2 g), if <60 kg - 1332 mg/day; Use for 6 months or longer; Reduce dose in moderate renal failure	Nausea, diarrhea, anorexia, flatulence, pruritus, dry mouth, paraesthesia, fatigue	Renal impairment, Hypercalcemia
Disulfiram	250-500 mg/day; Long-term use if required; Start 24 h after the last drink; Treatment most effective if well monitored and having good medication adherence	Nausea, vomiting, throbbing headaches, drowsiness, lethargy, peripheral neuropathy, optic neuritis, hepatotoxicity, psychosis	Liver disease, Active alcohol use, Psychosis, Cardiovascular disease
Non-FDA Approved Pharmacotherapy			
Topiramate	Initially 25 mg; increased to 300 mg twice a day in divided doses.	Dizziness, Anorexia, Anxiety, Diarrhea, Fatigue, Fever, Weight loss, Cognitive impairment.	Liver disease, Renal impairment, Metabolic acidosis, Renal calculi, Secondary angle closure glaucoma, Pregnancy (fetal harm)
Gabapentin	300-1800 mg per day	Dizziness, Fatigue, Peripheral edema, Nystagmus, Constipation, Ataxia	Renal impairment Potential for abuse
Nalmefene	18 mg per day	Gastric side effects, Perceptual disturbances	Active opioid use Liver disease Renal impairment
Baclofen	20-80 mg daily	Sedation, fatigue, sleep disorders, vertigo, dizziness, seizures, mania, sleep apnoea	Renal impairment
Ondansetron	4 mcg per kg twice a day	Anxiety, serotonin syndrome, malaise, fatigue, Dizziness	QTc prolongation Serotonin syndrome
Varenicline	2 mg per day	Fatigue, Nausea, somnolence	Hostility experience, agitation, depression, suicidal thoughts, stroke

g) Ondansetron: It is a serotonin-3 ($5HT_3$) receptor antagonist used to treat nausea and has shown to be efficacious in subjects with early-onset AUD. In a clinical trial, patients with AUD and the long LL genotype of the 5HT transporter promoter markedly reduced their alcohol drinking, and those with the TT genotype reduced their alcohol drinking even more. This study demonstrated the heterogeneity of AUD and the necessity for a personalized medicine approach.[17,73,80] Moreover, ondansetron markedly reduced daily drinking in light drinkers and without any benefit in heavy drinkers (>10 drinks/day).[79]

h) Varenicline: It is an FDA-approved medication for smoking cessation and several clinical trials provided its potential use in the management of AUD in individuals who smoke. It is a partial

agonist at α4β2, α3β2, and α6 nicotinic acetylcholine receptors (nAChRs) and an agonist of α3β4 and α7 nAChRs.[9,73,81] In clinical trials, varenicline reported a lower weekly percentage of heavy drinking days, fewer drinks per drinking day, and reduced craving for alcohol. Notably, it showed similar beneficial effects of reduced alcohol consumption and craving in both smokers and non-smokers and is considered as an effective pharmacotherapy for individuals who do and do not smoke.[9,61,81] Based on these results, it is prescribed off-labeled to treat AUD.[9,67,73]

10.3.3. Emerging pharmacotherapeutic agents

Novel agents that have been tested and undergoing investigation are ABT-436 (Highly selective vasopressin type 1B (VR_{1B}) receptor antagonist), GET73 (GHB analog; negative allosteric modulator at mGluR5), ASP8062 (Positive allosteric modulator of $GABA_B$ receptor), PF-5190457 (Ghrelin receptor inverse agonist), apremilast (Phosphodiesterase type 4 (PDE-4) inhibitor), cannabidiol (Cannabinoid CB_1 agonist with diverse pharmacological effects), pexacerfont and verucerfont (Corticotropin-releasing factor (CRF) receptor 1 antagonist), citicoline (Metabolite and precursor of acetylcholine), ifenprodil (G protein-activated inwardly rectifying potassium channel inhibitor), ketamine (High-affinity noncompetitive NMDA receptor antagonist), probenecid (Pannexin-1 channels inhibitor), 3,4-methylenedioxymethamphetamine (MDMA), suvorexant (Orexin receptors antagonist), and probiotics and fecal microbiota transplantation.[35-37,50,60,61,66,67,73,82,83]

CONCLUSION

AUDs are more common and at present worldwide it is one of the leading causes of death. AUDs include both alcohol dependence and alcohol abuse, further, AUDs are categorized into mild, moderate, and severe. The normal range of alcohol in the blood is 0.08 g% and if it increases in the blood may result in some physiological effects, such as euphoria, emotional swings, depression, loss of consciousness, vomiting, and alcohol intoxication. CAGE and AUDIT are screening tools to diagnose AUDs recommended by the WHO and widely used in clinical practice. Psychosocial therapies in combination with pharmacotherapy have shown to be beneficial. The first-line drugs to manage AUD are naltrexone and acamprosate, followed by disulfiram, the second-line agent. Besides, off-labeled drugs, such as topiramate, gabapentin, nalmefene, baclofen, ondansetron, and varenicline are also recommended in certain countries. Promoting social awareness, community health check-ups, public health campaigns, and utilization of evidence-based therapeutic options are imperative to effective management and successful recovery from AUDs.

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REFERENCES

1. Clites BL, Hofmann HA, Pierce JT. The promise of an evolutionary perspective of alcohol consumption. Neurosci Insights. 2023 Apr 4; 18:26331055231163589.
2. MacKillop J, Agabio R, Feldstein Ewing SW, et al. Hazardous drinking and alcohol use disorders. Nat Rev Dis Primers. 2022;8(1):80.
3. Global status report on alcohol and health 2018. Geneva: World Health Organization; 2018. Licence: CC BY-NC-SA 3.0. IGO. Available from: https://iris.who.int/bitstream/handle/10665/274603/9789241565639-eng.pdf?sequence=1. Accessed 18 January 2024.

4. GBD 2016 Alcohol and Drug Use Collaborators. The global burden of disease attributable to alcohol and drug use in 195 countries and territories, 1990-2016: a systematic analysis for the Global Burden of Disease Study 2016. Lancet Psychiatry. 2018;5(12):987-1012.
5. Ray LA, Bujarski S, Grodin E, et al. State-of-the-art behavioral and pharmacological treatments for alcohol use disorder. Am J Drug Alcohol Abuse. 2019;45(2):124-140.
6. SAMHSA, Center for Behavioral Health Statistics and Quality. 2022 National Survey on Drug Use and Health. Table 5.1A - Substance use disorder for specific substances in past year: among people aged 12 or older; by age group, numbers in thousands, 2021 and 2022. Available from: https://www.samhsa.gov/data/sites/default/files/reports/rpt42728/NSDUHDetailedTabs2022/NSDUHDetailedTabs2022/NSDUHDetTabsSect5pe2022.htm#tab5.1a. Accessed 18 January 2024.
7. Balasubramani K, Paulson W, Chellappan S, et al. Epidemiology, hot spots, and sociodemographic risk factors of alcohol consumption in indian men and women: analysis of National Family Health Survey-4 (2015-16), a Nationally Representative Cross-Sectional Study. Front Public Health. 2021;9:617311.
8. Glantz MD, Bharat C, Degenhardt L, et al. The epidemiology of alcohol use disorders cross-nationally: Findings from the World Mental Health Surveys. Addict Behav. 2020;102:106128.
9. Swift RM, Aston ER. Pharmacotherapy for alcohol use disorder: current and emerging therapies. Harv Rev Psychiatry. 2015;23(2):122-33.
10. Bardach AE, Alcaraz AO, Ciapponi A, et al. Alcohol consumption's attributable disease burden and cost-effectiveness of targeted public health interventions: a systematic review of mathematical models. BMC Public Health. 2019;19(1):1378.
11. Understanding alcohol use disorder. Available from: https://www.niaaa.nih.gov/publications/brochures-and-fact-sheets/understanding-alcohol-use-disorder. Accessed 18 January 2024.
12. Alcohol Use Disorder: A Comparison Between DSM–IV and DSM–5. Available from: https://www.niaaa.nih.gov/publications/brochures-and-fact-sheets/alcohol-use-disorder-comparison-between-dsm. Accessed 18 January 2024.
13. Safiri S, Nejadghaderi SA, Noori M, et al. Burden of diseases and injuries attributable to alcohol consumption in the Middle East and North Africa region, 1990-2019. Sci Rep. 2022;12(1):19301.
14. Wood AM, Kaptoge S, Butterworth AS, et al. Risk thresholds for alcohol consumption: combined analysis of individual participant data for 599 912 current drinkers in 83 prospective studies. Lancet. 2018 Apr 14;391(10129):1513-1523.
15. Tian Y, Liu J, Zhao Y, et al. Alcohol consumption and all-cause and cause-specific mortality among US adults: prospective cohort study. BMC Med. 2023;21(1):208.
16. Editorial staff. Drinking patterns and their definitions. Alcohol Research: Current Reviews. 2018. 39 (1): e1-e2. Available from: https://arcr.niaaa.nih.gov/media/581/download?inline. Accessed 18 January 2024.
17. Australian guidelines to reduce health risks from drinking alcohol. 2020. National Health and Medical Research Council. Commonwealth of Australia, Canberra. Available from: https://www.nhmrc.gov.au/sites/default/files/2022-07/Australian-guidelines-to-reduce-health-risks-from-drinking-alcohol.pdf. Accessed 18 January 2024.
18. Drinking levels defined. Alcohol's effects on health. research-based information on drinking and its impact. Available from: https://www.niaaa.nih.gov/alcohol-health/overview-alcohol-consumption/moderate-binge-drinking. Accessed 18 January 2024.
19. Dietary Guidelines for Americans 2015–2020. 8th ed. Washington, DC: U.S. Department of Health and Human Services and U.S. Department of Agriculture; December 2015. Available from http://health.gov/dietaryguidelines/2015/guidelines. Accessed 18 January 2024.
20. Snetselaar LG, de Jesus JM, DeSilva DM, Stoody EE. Dietary Guidelines for Americans, 2020-2025: Understanding the scientific process, guidelines, and key recommendations. Nutr Today. 2021;56(6): 287-295.

21. Substance Abuse and Mental Health Services Administration, Center for Behavioral Health Statistics and Quality. Key Substance Use and Mental Health Indicators in the United States: Results from the 2015 National Survey on Drug Use and Health. Rockville, MD: U.S. Department of Health and Human Services. Available from: https://www.samhsa.gov/data/sites/default/files/NSDUH-FFR1-2015/NSDUH-FFR1-2015/NSDUH-FFR1-2015.pdf. Accessed 18 January 2024.
22. Dasgupta A. "Alcohol a double-edged sword: Health benefits with moderate consumption but a health hazard with excess alcohol intake", in Dasgupta A (ed.), Alcohol, Drugs, Genes, and the Clinical Laboratory: An Overview for Healthcare and Safety Professionals, Academic Press, pp. 1–21.
23. Varghese J, Dakhode S. Effects of Alcohol Consumption on Various Systems of the Human Body: A Systematic Review. Cureus. 2022;14(10):e30057.
24. Alcohol Use Disorder. Available from: https://my.clevelandclinic.org/health/diseases/3909-alcoholism. Accessed on 19 January 2024.
25. Assessment tools used to diagnose alcohol use disorders. Available from: https://americanaddictioncenters.org/alcohol/assessment. Accessed on 19 January 2024.
26. Alcohol use disorder. Symptoms & causes. Available from: https://www.mayoclinic.org/diseases-conditions/alcohol-use-disorder/symptoms-causes/syc-20369243. Accessed 19 January 2024.
27. The steps to addiction: Stages of alcoholism. Available from: https://www.priorygroup.com/blog/stages-of-alcoholism. Accessed on 18 January 2024.
28. Four stages of alcoholism. Available from: https://sunhouston.com/stages-of-alcoholism/. Accessed on 18 January 2024.
29. What is the Jellinek Curve? Available from: https://www.therecoveryvillage.com/drug-addiction/what-is-jelinek-curve/. Accessed 18 January 2024.
30. Gough G, Heathers L, Puckett D, et al. The utility of commonly used laboratory tests to screen for excessive alcohol use in clinical practice. Alcohol Clin Exp Res. 2015; 39(8):1493-500.
31. Fakhari S, Waszkiewicz N. Old and new biomarkers of alcohol abuse: narrative review. J Clin Med. 2023;12(6):2124.
32. Trius-Soler M, Praticò G, Gürdeniz G, et al. Biomarkers of moderate alcohol intake and alcoholic beverages: a systematic literature review. Genes Nutr. 2023;18(1):7.
33. Fiellin DA, Reid MC, O'Connor PG. Screening for alcohol problems in primary care: a systematic review. Arch Intern Med. 2000;160(13):1977-89.
34. Higgins-Biddle JC, Babor TF. A review of the Alcohol Use Disorders Identification Test (AUDIT), AUDIT-C, and USAUDIT for screening in the United States: Past issues and future directions. Am J Drug Alcohol Abuse. 2018;44(6):578-586.
35. Arab JP, Izzy M, Leggio L, et al. Management of alcohol use disorder in patients with cirrhosis in the setting of liver transplantation. Nat Rev Gastroenterol Hepatol. 2022;19(1):45-59.
36. Kranzler HR, Soyka M. Diagnosis and pharmacotherapy of alcohol use disorder: a review. JAMA. 2018;320(8):815-824
37. Fairbanks J, Umbreit A, Kolla BP, et al. Evidence-based pharmacotherapies for alcohol use disorder: clinical pearls. Mayo Clin Proc. 2020;95(9):1964-1977.
38. Donato S, Ray LA. Neurobiology and the treatment of alcohol use disorder: a review of the evidence base. Subst Abuse Rehabil. 2023;14:157-166.
39. Yang W, Singla R, Maheshwari O, et al., Alcohol use disorder: neurobiology and therapeutics. Biomedicines. 2022;10(5): 1192.
40. Poorman E, McQuade BM, Messmer S. Medications for alcohol use disorder. Am Fam Physician. 2024;109(1):71-78.
41. Carpenter JE, LaPrad D, Dayo Y, DeGrote S, Williamson K. An overview of pharmacotherapy options for alcohol use disorder. Fed Pract. 2018t;35(10):48-58.
42. Ceci FM, Francati S, Ferraguti G, et al. Behavioral dysregulations by chronic alcohol abuse. Motivational enhancement therapy and cognitive behavioral therapy outcomes. Riv Psichiatr. 2022;57(1):1-9
43. Barré T, Ramier C, Antwerpes S, et al. A novel community-based therapeutic education program for reducing alcohol-related harms and stigma in people with

alcohol use disorders: A quasi-experimental study (ETHER study). Drug Alcohol Rev. 2023;42(3):664-679.
44. Lee IS, Lee M, Kim HK, Lee EJ. Effectiveness of a drinking-reduction program on drinking behavior, stages of change, drinking refusal self-efficacy, and resilience in Koreans with moderate alcohol use disorder. Arch Psychiatr Nurs. 2019; 33(2):189-195.
45. Song EA, Kim HK, Lee M. Effectiveness of therapeutic community program on resilience and change in lifestyle in people with alcohol use disorder. J Addict Nurs. 2022;33(4):255-263.
46. Huang Y, Chen X. Efficacy of group music therapy based on emotion-regulation skills on male inpatients with alcohol dependence: A randomized, controlled pilot trial. Front Psychol. 2021;12:697617.
47. Alcohol use disorder. Diagnosis & treatment. Available from: https://www.mayoclinic.org/diseases-conditions/alcohol-use-disorder/diagnosis-treatment/drc-20369250. Accessed 18 January 2024.
48. Coriale G, Fiorentino D, De Rosa F, et al. Treatment of alcohol use disorder from a psychological point of view. Riv Psichiatr. 2018;53(3):141-148.
49. Kelly JF, Abry A, Ferri M, Humphreys K. Alcoholics Anonymous and 12-step facilitation treatments for alcohol use disorder: a distillation of a 2020 Cochrane review for clinicians and policy makers. Alcohol Alcohol. 2020;55(6):641-651.
50. Witkiewitz K, Litten RZ, Leggio L. Advances in the science and treatment of alcohol use disorder. Sci Adv. 2019;5(9):eaax4043.
51. Manning V, Piercy H, Garfield JBB, et al. A personalized approach bias modification smartphone App ("SWiPE") to reduce alcohol use: open-label feasibility, acceptability, and preliminary effectiveness study. JMIR Mhealth Uhealth. 2021;9(12):e31353.
52. McKay JR, Gustafson DH, Ivey M, et al. Efficacy and comparative effectiveness of telephone and smartphone remote continuing care interventions for alcohol use disorder: a randomized controlled trial. Addiction. 2022;117(5):1326-1337.
53. Abrantes AM, Meshesha LZ, E Blevins C, et al. A smartphone physical activity app for patients in alcohol treatment: single-arm feasibility trial. JMIR Form Res. 2022;6(10):e35926.
54. Leightley D, Williamson C, Rona RJ, et al. Evaluating the efficacy of the Drinks:Ration mobile app to reduce alcohol consumption in a help-seeking military veteran population: randomized controlled trial. JMIR Mhealth Uhealth. 2022;10(6):e38991.
55. Starbird LE, Gutkind S, Teixeira P, et al. Economic cost of the HealthCall smartphone intervention to reduce heavy alcohol drinking in adults with HIV. J Stud Alcohol Drugs. 2023;84(6):814-822.
56. Liu SW, You CW, Fang SC, et al. A smartphone-based support system coupled with a bluetooth breathalyzer in the treatment of alcohol dependence: A 12-week randomized controlled trial. Internet Interv. 2023;33:100639.
57. Li S, Zhang D, Liu J, et al. The preliminary efficacy of virtual agent-assisted intelligent rehabilitation treatment (Echo app v2.0) in patients with alcohol use disorders: Study protocol for a randomized controlled trial. Digit Health. 2023;9:20552076231219432.
58. Ekhtiari H, Tavakoli H, Addolorato G, et al. Transcranial electrical and magnetic stimulation (tES and TMS) for addiction medicine: A consensus paper on the present state of the science and the road ahead. Neurosci Biobehav Rev. 2019;104:118-140.
59. Coe C, Patel A, Lawrence D. Pharmacotherapy options for alcohol use disorder in patients with alcohol-associated liver disease: a brief guide for clinicians. Clin Liver Dis (Hoboken). 2023;21(5):125-129.
60. Koob GF. Alcohol use disorder treatment: problems and solutions. Annu Rev Pharmacol Toxicol. 2024;64:255-275.
61. Burnette EM, Nieto SJ, Grodin EN, et al. Novel agents for the pharmacological treatment of alcohol use disorder. Drugs. 2022;82(3):251-274.
62. Stokłosa I, Więckiewicz G, Stokłosa M, et al. Medications for the treatment of alcohol dependence-current state of knowledge and future perspectives from a public health perspective. Int J Environ Res Public Health. 2023;20(3):1870.
63. Dunn KE, Bird HE, Bergeria CL, et al. Operational definition of precipitated opioid withdrawal. Front Psychiatry. 2023; 14:1141980.

64. Hyland SJ, Brockhaus KK, Vincent WR, et al. Perioperative pain management and opioid stewardship: a practical guide. healthcare (Basel). 2021;9(3):333.
65. Donoghue K, Hermann L, Brobbin E, Drummond C. The rates and measurement of adherence to acamprosate in randomised controlled clinical trials: A systematic review. PLoS One. 2022;17(2):e0263350.
66. Winslow BT, Onysko M, Hebert M. Medications for alcohol use disorder. Am Fam Physician. 2016;93(6):457-65.
67. Lohoff FW. Pharmacotherapies and personalized medicine for alcohol use disorder: a review. Pharmacogenomics. 2020;21(15):1117-1138.
68. Mong J, Ahamad K, Bach P. Anticraving medication for moderate to severe alcohol use disorder. CMAJ. 2021;193(19):E695.
69. Lanz J, Biniaz-Harris N, Kuvaldina M, et al. Disulfiram: mechanisms, applications, and challenges. Antibiotics (Basel). 2023;12(3):524.
70. Farokhnia M, Rentsch CT, Chuong V, et al. Spironolactone as a potential new pharmacotherapy for alcohol use disorder: convergent evidence from rodent and human studies. Mol Psychiatry. 2022;27(11):4642-4652.
71. Flanagan JC, Nietert PJ, Sippel L, et al. A randomized controlled trial examining the effects of intranasal oxytocin on alcohol craving and intimate partner aggression among couples. J Psychiatr Res. 2022;152:14-24.
72. Goh ET, Morgan MY. Review article: pharmacotherapy for alcohol dependence - the why, the what and the wherefore. Aliment Pharmacol Ther. 2017;45(7):865-882.
73. Morley KC, Perry CJ, Watt J, et al. New approved and emerging pharmacological approaches to alcohol use disorder: a review of clinical studies. Expert Opin Pharmacother. 2021;22(10):1291-1303.
74. Fortinguerra F, Pierantozzi A, Trotta F. The use of medications approved for alcohol use disorders in Italy. Front Public Health. 2023;11:1110435
75. Guiraud J, Addolorato G, Aubin HJ, et al. Sodium oxybate for alcohol dependence: a network meta-regression analysis considering population severity at baseline and treatment duration. Alcohol Alcohol. 2023;58(2):125-133.
76. Di Miceli M, Gronier B. Pharmacology, systematic review and recent clinical trials of metadoxine. Rev Recent Clin Trials. 2018;13(2):114-125.
77. Higuera-de la Tijera F, Servín-Caamaño AI, Serralde-Zúñiga AE, et al. Metadoxine improves the three- and six-month survival rates in patients with severe alcoholic hepatitis. World J Gastroenterol. 2015;21(16):4975-85.
78. Sinclair JMA, O'Neill A. Update on the management of alcohol use disorders. BJPsych Advances. 2020;26(2):82–91.
79. Wackernah RC, Minnick MJ, Clapp P. Alcohol use disorder: pathophysiology, effects, and pharmacologic options for treatment. Subst Abuse Rehabil. 2014;5:1-12.
80. Johnson BA, Seneviratne C, Wang XQ, et al. Determination of genotype combinations that can predict the outcome of the treatment of alcohol dependence using the 5-HT(3) antagonist ondansetron. Am J Psychiatry. 2013;170(9):1020-31.
81. Mitchell JM, Teague CH, Kayser AS, et al. Varenicline decreases alcohol consumption in heavy-drinking smokers. Psychopharmacology (Berl). 2012;223(3):299-306
82. Grigsby KB, Mangieri RA, Roberts AJ, et al. Preclinical and clinical evidence for suppression of alcohol intake by apremilast. J Clin Invest. 2023;133(6):e159103.
83. Wolstenholme JT, Duong NK, Brocato ER, Bajaj JS. Gut-liver-brain axis and alcohol use disorder: treatment potential of fecal microbiota transplantation. Alcohol Res. 2024;44(1):01.

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