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A Systematic Review for Advanced Solutions for Alcohol Use Disorder: Detection, Treatment, and Prevention

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ABSTRACT

Alcohol consumption is widespread worldwide, impacting various medical, psychological, and community outcomes. Alcoholism is a major risk factor for alcohol use disorder (AUD), a significant health condition with increasing mortality rates. The DSM of Mental Disorders IV edition diagnoses AUD, and symptoms vary in severity. Treatment approaches include pharmacological interventions like naltrexone, acamprosate, disulfiram, and emerging medications like topiramate, varenicline, and ondansetron. Digital interventions, such as mobile applications and artificial intelligence, offer new opportunities to support individuals with AUD, particularly in remote areas. Biochemical measurements can objectively evaluate alcohol use, but none are perfect. Additional experimental markers, such as sialic acid and byproducts like acetaldehyde and fatty acid ethyl esters (FAEE), can help measure relapse and acute alcohol consumption. Comprehensive treatment programs integrating behavioral help, digital tools, and pharmacotherapies are crucial for recovery and preventing relapse. This review critically evaluates blood biomarkers research and treatment response of AUD and challenges facing them.

Key words: alcohol use disorder, biomarkers, treatment response, challenges, mental Disorders.

Introduction

Excessive alcohol intake can have serious health consequences, including alcohol use disorder (AUD). AUD is a long-term disorder marked by an obsessive desire for alcohol in spite of its harmful effects on one's health and social well-being [1]. Individuals with AUD often struggle to control their alcohol intake, leading to a loss of control and experiencing negative emotions when alcohol is not readily available [2, 3]. AUD can progress from intermittent binge drinking to prolonged heavy drinking, which leads to constant drinking for fear of withdrawal [4]. The Diagnostic and Statistical Manual of Mental Disorders, 5th edition (DSM-5) [5] defines AUD as positive findings on at least 2 of 11 criteria, which provides a framework for symptom intensity relative to symptom number. Under the new term AUD, the DSM-5 combines earlier diagnostic criteria for alcohol abuse and dependence with severity modifiers of mild, moderate, and severe based on the number of criteria met. DSM-5 classifies AUD as a spectrum disorder [4].

Mortality due to AUD has increased annually, highlighting the need to prevent or treat this condition of uncontrolled drinking [6]. It has been reported that the psychological and physical impacts of alcohol are markedly promoted by ethanol metabolites, making ethanol metabolism critical to understanding AUD [7].

In the presence of O_2 (aerobic respiration), ethanol undergoes oxidative metabolism by multiple enzymes, depending on where the reaction occurs inside the cell (Fig. 1). The liver and stomach are the primary organs involved in the initial metabolism of ethanol. In the cytosol of hepatocytes, the main detoxification pathway of ethanol is done by alcohol dehydrogenase 1 (ADH-1) oxidizing ethanol into acetaldehyde (ACH) and reducing NAD+ to NADH. These reactions expose liver cells to potential injury from the acetaldehyde and free radicals, which are

byproducts of ethanol metabolism (Fig. 1) [8]. The major inducible pathway, mediated by the CYT2E1 enzyme in the liver and tissues with low ADH activity, such as the brain, metabolizes ethanol, forming ACH and other reactive species like hydroxyl radicals and superoxide anion. A minor route of alcohol oxidation also occurs in the peroxisomes of hepatocytes and brain cells, catalyzed by catalase (Fig. 1). The formed ACH is quickly metabolized in the mitochondria by ADH-2 to generate acetate. The acetate is then eliminated in the circulation for entering other pathways to produce energy [8].

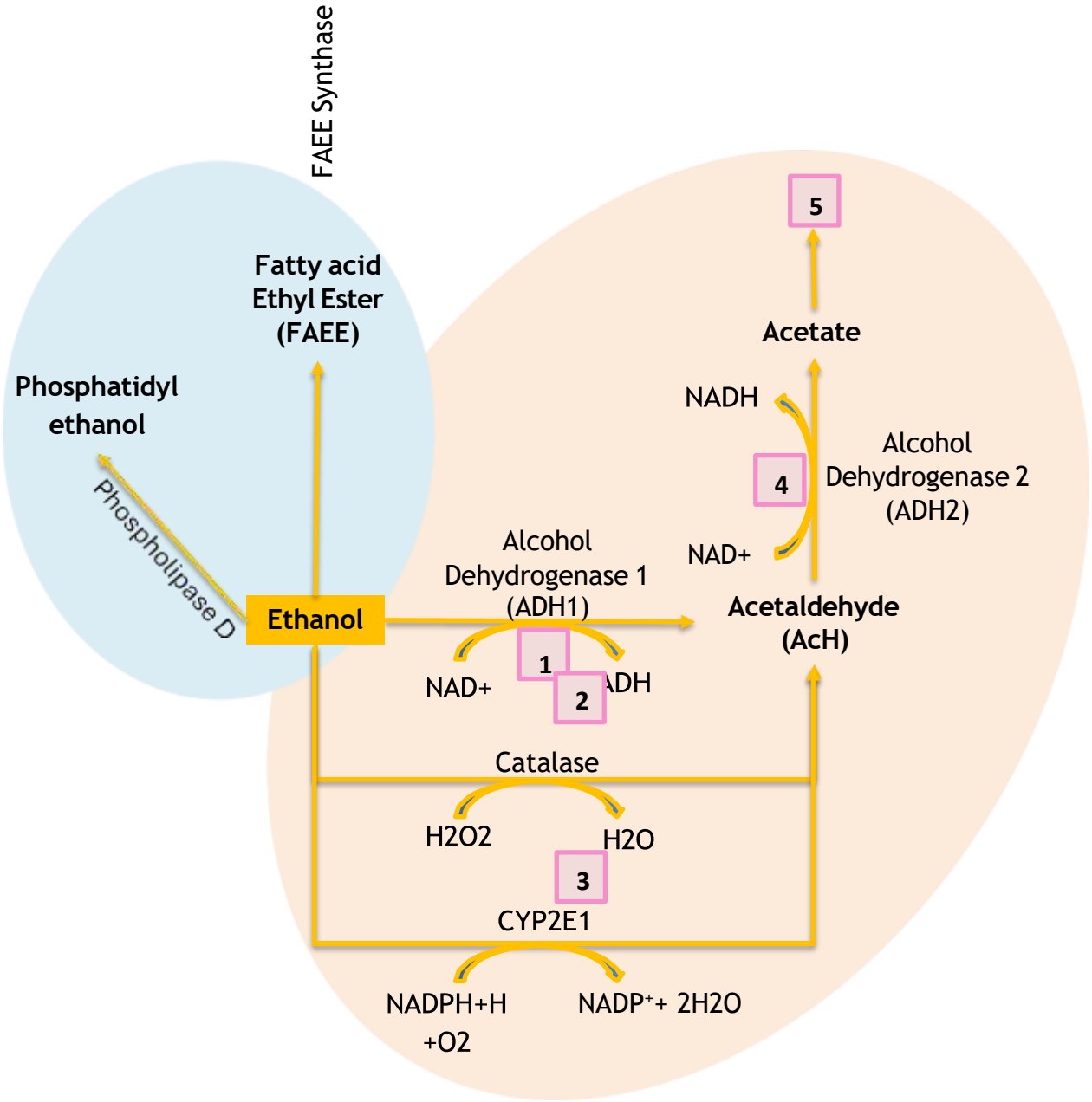

Fig. 1 Possible mechanisms in ethanol metabolism [8]

In the absence of O_2 (anaerobic respiration) or the enzymes of the oxidative pathway inhibited, ethanol undergoes two nonoxidative metabolic pathways, and its outcomes may have pathological and diagnostic significance. The enzyme that catalyzed the reaction of the first pathway is fatty acid ethyl esters (FAEEs) synthase [9]. It enhances the esterification process of fatty acids and weak organic acids with alcohol to form FAEE, which has several functions in the cell. FAEEs in alcohol abuse induced tissue damage. The second nonoxidative pathway is catalyzed by phospholipase D (PLD) forming phosphatidyl ethanol (PEth) (Fig. 1) [10]. The metabolism and elimination of phosphatidyl ethanol are very poor, so this product accumulates and disrupts the cell signaling pathways of the cell. The serum FAEEs and phosphatidyl ethanol are good indicators to detect alcohol ingestion [9, 10].

The ACH is responsible for the formation of ACH adducts, which are the results of binding ACH to other macromolecules such as lipids, proteins, and nucleic acids. The ACH adducts can alter the structure and role of these compounds, progressing carcinogenesis. To overcome the side effect of ACH, mitochondria metabolized this compound, forming acetate, which undergoes further reactions for giving energy by entering the Krebs cycle or forming fatty acid, which is the main cause of alcoholic fatty liver [8, 11]. The CYT2E1 pathway induces the production of free radicals which induce oxidative damage to the liver. Genetic polymorphisms in the ADH have been linked to an increased risk of AUD, suggesting that ethanol metabolism is a crucial factor in the enhancement of this condition. In this review, we will explore the detection, treatment potential, and prevention of AUD [12].

Methods

For the purpose of conducting a literature review, the following search terms were used in the MEDLINE medical database via PubMed: "Alcohol use disorder" "diagnostic criteria of Alcohol use disorder," " severity of alcoholic consumption of Alcohol use disorder " "clinical manifestations," " Alcohol use disorder treatment," "adherence to therapy," "laboratory investigation," and " Challenges in management and possible solutions." In an effort to include as much of the existing literature as possible, the references of the discovered articles underwent additional evaluation. The selection of articles was based on their emphasis on Alcohol use disorder.

Results

1. The Cycle of AUD and Its Diagnostic Criteria

A chronic, recurrent condition associated with obsessive drinking, an inability to control alcohol intake, and the emergence of negative emotional states when alcohol is not used is known as alcohol use disorder (AUD) [2, 4]. Alcohol use in AUD can vary from intermittent episodes of heavy drinking to continuous heavy drinking over extended periods, often progressing to persistent drinking due to fear of withdrawal. The diagnosis of AUD is based on meeting at least two of the 11 criteria outlined in the Diagnostic and Statistical Manual (DSM) of Mental Disorders IV edition, which provides a framework for assessing symptom severity based on the number of symptoms an individual experiences. The severity of the disorder is classified as mild, moderate, or severe, depending on the number of criteria met. According to the DSM framework, an individual may enter the addiction cycle at various stages. Typically, individuals with AUD may begin with occasional heavy drinking during the binge/intoxication phase and progress to the withdrawal/negative affect phase, driven by aversive consolidation. However, many alcohol abusers may also start with adverse consolidation as the primary motivator, either through self-medication or chronic pain [4].

A three-phase cycle—binge/intoxication, withdrawal/negative impact, and preoccupation/anticipation—is a frequently cited framework for AUD and addiction. This model aids in comprehending the intricacy of AUD, particularly in light of various treatment modalities

[4, 13]. This framework identifies three major domains in which dysfunction arises: executive function, negative emotional states, and incentive salience and habitual behaviors. The prefrontal cortex, extended amygdala, and basal ganglia are the three main brain regions that these regions are connected to, in that order. These phases build upon one another as time goes on, eventually resulting in the development of AUD. From an alternative angle, joining the cycle at any point can cause neuroadaptations that lead to an obsession with alcohol. The theory goes that excessive alcohol stimulation of the brain's reward system upsets normal hedonic balance, triggering compensatory responses in the reward and stress circuits of the brain. These responses then add to the negative affect stage of withdrawal, which is linked to the negative emotional state. Concurrently, there is a decline in executive function, resulting in deficiencies that support the preoccupation or anticipation stage. This impairment feeds the cycle of addiction by increasing cravings for alcohol [14].

2. Screening Instruments

"When initial assessments and interviews indicate potential alcohol misuse, further evaluation should be conducted using standardized screening questionnaires. Numerous instruments are available to assess for alcohol-related problems."The three that are most widely used and validated are the Cut, Annoyed, Guilty, and Eye (CAGE) Questionnaire [15], the Michigan Alcoholism Screening Test (MAST) [16], and the Alcohol Use Disorders Identification Test (AUDIT) [17]. The CAGE is preferred for use in older adults [18, 19].

3. Diagnosis of severity of alcoholic consumption of AUD patients

3.1. Liver enzymes

The liver is the factory where alcohol metabolism takes place, so it is the first organ affected by alcohol consumption overdose. Any elevation in the activities of liver enzymes; ALT, AST, and GGT resemble any hepatic damage [12, 20].

3.2. Mean Corpuscular Volume (MCV)

The mean corpuscular volume (MCV) in heavy drinkers is typically higher than the average range, which is associated with heavy chronic drinking [21]. As a biomarker for alcohol consumption, clinicians have utilized mean corpuscular volume (MCV), which is the mean volume of red blood cells. There are several factors that contribute to enlarged red blood cells in heavy drinkers. These include the direct toxic effects of alcohol and its metabolites on red blood cells and bone marrow, interactions with erythrocyte metabolism, and inadequate nutrition, which includes deficiencies in folate and vitamin B12 [22]. An elevated MCV could suggest excessive alcohol consumption, which is 60 grams or more per day. The MCV of excessive drinkers is slightly higher, and it remains high even after a short period of abstinence (about 2-4 months) [23, 24].

3.3. β-Hexosaminidase

All cells contain the lysosomal enzyme β-Hexosaminidase. Its role is essential for the breakdown of glycoproteins [25]. Heavy alcohol consumption breaks down lysosomal because it allows the enzyme to leak into bodily fluids [26, 27]. Serum, saliva, urine, and other bodily fluids can all have their enzyme activity measured. However, people who have myocardial cerebral infarction, diabetes, cirrhosis, hypertension, cholestasis, pregnancy, or cholestasis may receive false-positive results from the β-Hexosaminidase enzyme activity [27]. In certain preliminary research, it has been shown to be a sensitive and specific indicator of binge drinking, and it is discovered to be higher in high drinkers. Additionally, whereas MCV returns to normal after 7–10 days of abstinence, increased β-Hexosaminidase does not [26].

3.4. Carbohydrate-deficient transferrin (CDT)

The increment of carbohydrate-deficient desialylated transferrin (CDT) isoforms is a specific indicator in diagnosing AUD individuals where alcohol and its metabolites inhibit sialyltransferase enzyme activity and activate sialidase and disturb the elimination of transferrin, so heavy alcohol drinking increases the levels of CDT isoforms [25, 28]. These isoforms are very sensitive in monitoring abstinence. But CDT has low sensitivity (>45%) in females, young people, and overdo drinkers, even at fit persons. Specified disorders can decrease the confidence of the CDT test, including HCV, HCC, chronic active hepatitis, primary biliary cirrhosis, genetic glycoprotein deficiency condition, galactosemia, insulin-related metabolic syndromes, cystic fibrosis, and anal cancer [28].

3.5. Fatty acid ethyl esters (FAEEs)

Latest findings have demonstrated that FAEEs are sensitive and definite indicators for differentiating between different types of drinkers where ethyl oleate levels are increasing in chronic alcohol customers compared to rare binge drinkers [9, 10].

3.6. Phosphatidylethanol (Peth)

A relatively latest bioindicator specific to the presence of PEth (non-oxidative ethanol metabolite), which can distinguish alcohol levels in the serum after 2–4 weeks of drinking [9, 10]. The quantity of PEth in the blood rises with repetitive alcohol intake. That molecule is effective in differentiating between extreme and rational alcohol drinking [25].

3.7. Cytokeratin

Cytokeratin is a diagnostic and prognostic tool for alcoholic hepatitis because it indicates hepatocyte death. It was found that alcoholic hepatitis is accompanied by an increment in cytokeratin, so it's very important to include that biomarker in routine analysis for the detection of alcoholic hepatitis severity [29].

3.8. Total Serum Sialic Acid (TSA)

Given the obvious potential of sialic acid as a highly specific marker for alcohol use, researchers are considering testing total sialic acid (TSA) levels in patient blood rather than concentrating only on the variations in sialic acid chains on glycoproteins like transferrin and apolipoprotein J [24].

3.9. 5-Hydroxytryptophol (5-HTOL)

Alcohol consumption significantly increases the production of 5-hydroxytryptophol (5-HTOL) in the body. This metabolite is derived from the breakdown of serotonin, a neurotransmitter crucial for brain function. The typical metabolic routes of serotonin are disrupted by alcohol and its principal metabolite, acetaldehyde, which results in an increased synthesis of 5-HTOL [30].

3.10. Acetaldehyde

Acetaldehyde is the initial byproduct of alcohol metabolism. It is a free compound that can bind to specific proteins, one of which is hemoglobin, the oxygen-carrying protein in red blood cells. By utilizing high-performance liquid chromatography and fluorescence detection, specifically the whole blood-associated acetaldehyde assay (WBAA), researchers can determine the concentrations of free and bound acetaldehyde in blood samples [31].

3.11. Salsolinol

This substance is created when the neurotransmitter dopamine combines with either pyruvate, a metabolite of glucose used by cells as energy, or acetaldehyde, a byproduct of alcohol. It has some

potential as a state marker for chronic alcohol consumption. However, the method used to measure salsolinol—whether it be in brain tissue, blood, or urine, for example—may affect how beneficial it is. Salsolinol levels in the blood may give a more accurate picture of chronic alcohol consumption than salsolinol levels in the urine, which have been found to decline after acute alcohol consumption [32].

3.12. Ethyl glucuronide and Ethyl sulphate

Ethyl Glucuronide (EtG) is a metabolite of ethanol, formed in the liver as a result of alcohol consumption. This compound is a product of the conjugation of ethanol with glucuronic acid, a biological substance produced by the liver to facilitate the elimination of toxins and foreign substances from the body.EtG is a sensitive and reliable biomarker for recent alcohol use. Its presence in urine can indicate even relatively small amounts of alcohol consumption. The detection window for EtG can extend up to five days, depending on the specific cutoff level employed and the quantity of alcohol ingested. [32, 33, 34]. Ethyl sulfate (EtS), a primary metabolite of ethanol, is emerging as a promising biomarker for the detection of recent alcohol consumption. While it shares a comparable detection window with ethyl glucuronide (EtG), its unique metabolic pathways distinguish it. EtS is synthesized by sulfotransferases in the liver through a conjugation process involving activated sulfate and ethanol. Subsequently, it is excreted in urine. Unlike EtG, which is metabolized by glucuronidase, EtS is degraded by sulfatases [35].

3.13. Challenges facing testing of alcohol intake

In clinical and forensic contexts, determining recent alcohol consumption through traditional methods like clinical history and physical examination can be problematic due to factors such as denial or underreporting. While direct ethanol measurement provides a reliable indicator for immediate exposure, it rapidly diminishes from the body. For detecting more remote alcohol use, biomarkers like EtG and EtS are employed.However, the effectiveness of EtG and EtS in detecting remote alcohol use is subject to several limitations. The detection window for these biomarkers varies significantly based on factors such as the amount and timing of alcohol consumption, individual physiological characteristics (e.g., liver and kidney function), and underlying medical conditions. Additionally, laboratory parameters like analytic limits of detection and the chosen cutoff for positive/negative interpretation further influence the reliability of these biomarkers [36, 37, 38]. "EtG and EtS, metabolites of ethanol, can persist in urine for an extended period, particularly in individuals who consume alcohol heavily. This prolonged detection window offers a more comprehensive assessment of recent alcohol consumption compared to the detection of ethanol alone." [38]. "Both EtG and EtS are secondary metabolites of ethanol, with EtG typically exhibiting higher concentrations than EtS. However, individual variations in their formation can significantly influence these levels. It's important to note that EtG and EtS can also be detected following exposure to products like hand sanitizers, mouthwashes, or certain foods containing trace amounts of ethanol or its metabolites, such as non-alcoholic beverages, sauerkraut, and overripe bananas." [39]. "While commonly referred to as false-positives, a more accurate term for these instances is 'innocent positives.' These occur
when individuals exhibit detectable levels of ethanol or its metabolites, EtG and EtS, without having consumed alcoholic beverages. Research investigating typical use of products containing ethanol, such as hand sanitizer applied once per hour for eight hours, has generally shown EtG and EtS concentrations reaching approximately 50-100 ng/mL. More intensive use has been associated with higher concentrations, exceeding 500 ng/mL EtG, but may not be representative of everyday scenarios." [40]. EtG and EtS testing currently lacks standardized cutoffs or detection limits. This is due to the conflicting recommendations in the literature. While some studies propose higher cutoffs to minimize false positives, others advocate for lower detection limits to identify even minimal alcohol consumption. Factors such as measurement sensitivity and uncertainty have also

influenced cutoff definitions. The Substance Abuse and Mental Health Services Administration offers a widely recognized categorization of EtG concentrations into very low, low, and high positive levels, providing corresponding interpretations [41]. Ethanol biomarker testing, while crucial for medical and legal decisions, is often hindered by various preanalytic, analytic, and postanalytic factors. Ethyl Glucuronide (EtG), a commonly used biomarker, is susceptible to preanalytic issues that can lead to both false-positive and false- negative results. For instance, ex vivo formation in the presence of glucosuria or degradation in specimens stored at room temperature can significantly impact EtG detection. To mitigate these concerns, simultaneous measurement of EtG and Ethyl Sulfate (EtS) can provide increased confidence in results, as EtS is less prone to such preanalytic interferences. Furthermore, screening assays for EtG have been known to produce false-positives due to metabolites of other alcohols, such as propanol, and certain medications, including chloral hydrate. To ensure accurate interpretation of results, screen-positive samples should be confirmed using a definitive methodology like mass spectrometry (MS). This can help identify false-positives and provide more reliable data for decision-making. Given the critical role of ethanol biomarker testing in medical and legal contexts, it is imperative to address these preanalytic, analytic, and postanalytic challenges. The variability in biomarker detection and quantitation among laboratories can also influence the interpretation of EtG and EtS results. Therefore, standardized protocols and quality control measures are essential to ensure consistent and reliable outcomes [42, 43]. While elevated serum levels of (GGT) and transaminases ALT and AST are commonly associated with heavy alcohol consumption, the precise dose-response relationships between these biomarkers and ethanol intake remain unclear. Additionally, the impact of moderate alcohol
consumption on liver enzyme induction and the role of oxidative stress in GGT activity have been subjects of ongoing investigation. Recent studies suggest that GGT enzyme induction may be initiated at relatively low levels of ethanol exposure, indicating a gradual effect of alcohol on liver function. Moreover, while elevated liver enzymes and decreased hepatic proteins are often observed in advanced alcoholic liver disease, the specific biomarkers and their diagnostic utility in various stages of the disease continue to be explored. It is important to note that the presence of these biomarkers is indicative of ethanol exposure but does not necessarily confirm the consumption of alcoholic beverages. Further research is needed to elucidate the complex interplay between ethanol intake, liver enzymes, proteins, and oxidative stress in the context of alcoholic liver disease [44].

The Whole Blood-Associated Acetaldehyde Assay (WBAA) is a highly accurate and sensitive test capable of detecting heavy alcohol consumption [45]. It has been used in the insurance industry for over a decade and is currently under consideration for broader clinical applications. The WBAA assay measures the accumulation of acetaldehyde bound to hemoglobin in red blood cells, providing a snapshot of alcohol use over the past 120 days. An increase in WBAA assay results suggests ongoing alcohol consumption. Furthermore, elevated levels of protein-bound acetaldehyde persist for approximately a month after alcohol cessation, further reinforcing the test's value in assessing recent alcohol use. [31]. The WBAA assay's distinctive feature lies in its capacity to track alcohol consumption patterns longitudinally, setting it apart from other biomarkers.

Despite its high specificity for detecting heavy alcohol consumption, the CDT marker faces challenges in terms of accuracy and sensitivity. The prevalence of low CDT levels in non- drinkers and the challenge of adequately measuring and differentiating CDT from other transferrin isoforms can result in false positive and negative results. Moreover, gender-based differences in CDT levels and the relatively high rate of false negatives further limit its effectiveness as a screening tool. In order to overcome these constraints, scientists have concentrated on creating more accurate and sensitive techniques for quantifying CDT, like immunological reagents [47]. "Certain studies have explored the efficacy of measuring carbohydrate-deficient transferrin (CDT) levels as a percentage

of total transferrin rather than relying solely on absolute values. Additionally, some research has investigated the potential
benefits of combining CDT testing with gamma-glutamyl transferase (GGT) analysis." Discovering that using both tests is more sensitive than utilizing only one marker, at least in men [48, 49]. Javors and Johnson [26] found that both male and female alcoholics exhibited higher levels of TSA than their socially drinking counterparts. Their research indicated that comparable to the CDT test in terms of sensitivity and specificity, the TSA test measures alcohol intake. However, the TSA test might be less appropriate for treatment programs assessing patient relapse because of its slower decline during periods of abstinence compared to CDT or GGT.

The urinary excretion of 5-HTOL, a metabolite of 5-HT, persists for a significantly longer duration than that of alcohol. Specifically, 5-HTOL can be detected in the urine for 5 to 15 hours after consumption, while alcohol can be detected for only a little over an hour per drink. This suggests that 5-HTOL may serve as a more sensitive and prolonged marker of recent 5-HT activity compared to alcohol measurements [30]. 5-HTOL, a biomarker capable of identifying recent heavy alcohol consumption, has shown promise in preliminary studies. Given its special capacity to identify alcohol usage up to 24 hours after intake, it may prove to be an invaluable instrument for analyzing patterns of alcohol consumption. While further research is warranted, the initial findings indicate that 5-HTOL is both sensitive and specific in identifying individuals who have engaged in heavy drinking within the preceding day [58]. Emergency room clinicians may benefit from utilizing a test that identifies individuals who have consumed excessive amounts of alcohol prior to surgical preparation. Additionally, healthcare professionals working in treatment maintenance programs can potentially employ this test to monitor the progress of patients undergoing treatment. However, it is important to note that the anti-alcohol medication disulfiram, commonly used in these settings, can also elevate 5-HTOL levels. Moreover, studies indicate that the ratio of 5-HTOL to 5-HIAA, another serotonin metabolite, is a useful predictor of previous alcohol intake [50].

FAEE is a highly reliable biomarker that can differentiate between individuals who consume alcohol moderately and those who engage in excessive or problematic drinking patterns. [51, 52]. Due to its presence in human hair, FAEEs have been proposed as a potential biomarker for chronic excessive alcohol intake [51]. The persistent nature of FAEEs within hair, resulting from the body's inability to eliminate them, suggests their accumulation over extended periods of heavy alcohol consumption [53, 54].

Haber et al.'s [55] research revealed that even brief periods of abstinence (as short as a week) from alcohol consumption can lead to a reduction in salsolinol levels within lymphocytes of former alcoholics. This finding contrasts with studies examining salsolinol levels in the brain, which have failed to identify significant differences between alcoholics and non-alcoholics [56]. These discrepancies may be attributed to challenges associated with measuring salsolinol within the brain, as well as inherent variations in salsolinol concentrations across different biological tissues.

The clinical utility of the mean corpuscular volume (MCV) marker is limited due to its prolonged elevation following alcohol cessation and susceptibility to influence by other factors. Consequently, the specificity of MCV is compromised, potentially hindering the accurate interpretation of results based on this marker [24].

While an elevated MCV can be a potential indicator of excessive alcohol consumption, it is not a definitive or exclusive marker. Factors such as age, gender, and underlying health conditions must be carefully considered when interpreting MCV results. Previous studies have shown that MCV may be more sensitive to heavy alcohol use in women compared to men, while it may exhibit greater specificity in men than in women. [56, 57]. The presence of microcytosis and macrocytosis in alcohol-related conditions can result in a dimorphic anemia, leading to a normal average calculated MCV. This can occur in conditions like liver cirrhosis, malnutrition, and iron deficiency anemia, which are often associated with alcohol abuse. While non-alcohol-related conditions like megaloblastic anemia can also increase MCV, the combination of microcytosis and macrocytosis

is a strong indicator of alcohol-related anemia. Therefore, MCV should be evaluated in conjunction with other markers, such as gamma-glutamyl transferase (GGT) or phosphatidylethanol (PEth), to accurately assess alcohol consumption and its impact on hematological parameters [58, 59, 60].
The β-Hexosaminidase assay, while a valuable diagnostic tool, is often difficult to obtain in the United States. Consequently, clinicians have limited experience in its application across various patient populations. Additionally, other health conditions, such as diabetes and hypertension, have been shown to influence β-Hexosaminidase levels, further complicating its interpretation [26].
While (AST) and (ALT) are less reliable indicators of alcoholism than (GGT), they can still be elevated in individuals with excessive alcohol consumption. However, these enzymes are primarily used to assess liver damage rather than directly linking to alcohol intake. Notably, studies have shown that in individuals without underlying liver conditions, significant alcohol consumption can lead to an increase in AST and ALT levels within the bloodstream [38]. While both ALT and AST are elevated in cases of alcohol-induced liver injury, ALT is considered a more specific marker due to its predominant localization in the liver compared to AST, which is found in multiple organs. Significantly elevated levels of either enzyme, such as 500 units per liter, can suggest alcoholic liver disease. To aid in diagnosing heavy alcohol consumption, clinicians frequently assess the AST to ALT ratio. However, the accuracy of these markers may be limited in individuals under 30 or over 70 years of age, rendering them less reliable than other comprehensive diagnostic tools [24, 31].

4. AUD therapeutic approaches

AUD needs flexible therapeutic approaches [61]. AUD is usually associated with hepato-renal complications, depression, anxiety illnesses, malnutrition, bipolar syndromes, and other psychotic problems. To manage that condition, combined long-term improvement support is required [62]. Multidisciplinary extended support strategies are regularly applied to avoid relapse or deterioration when treating AUD and manage scale of social, psychological, and physical activities [62, 63]. "Despite the combined application of behavioral therapies such as cognitive- behavioral therapy and motivational enhancement therapy, along with standard healthcare practices, there were insufficient outcomes in initiating and maintaining abstinence among individuals with alcohol use disorder." [64].

4.1. Digital intervention technologies

Digital intervention technologies can offer new hope for reducing the burden of AUD. These digital interventions include mobile devices, instant messaging, apps, social media, artificial intelligence, and algorithms [64, 65]. Digital technologies can promote health behavior modification among patients, healthcare workers, caregivers, and the public, such as encouraging smoking cessation, healthy eating habits, and increased physical activity. Recently, digital technology has been used extensively to reduce AUD, inform about risks, and treat and monitor patients to prevent relapse. Digital technology has become a major and important tool for ensuring access to primary health care services, especially in the management and treatment of AUD [64]. Digital interventions and traditional treatments must be combined to finally eliminate these disorders [62]. Digital technology can play an important role in helping these cases overcome the psychological barrier, start treatment, adhere to it, and abstain from use. Digital interventions can also be used as a major tool for diagnosis and treatment and provide reliable models for collecting patient data and reducing morbidity and mortality associated with this condition [62, 66].

4.2. Comprehensive Approaches for Treating and preventing of AUD and Enhancing Liver Health: A Multidisciplinary Strategy

Improving liver health and preventing relapse in alcoholics using drug treatment for addiction is a given, but treatment with acamprosate is prohibited because previous studies have shown that it is associated with harmful effects related to the liver. However, the optimal solution, despite its difficulty, is for the alcoholic to challenge himself and abstain from drinking alcohol. From here, unexpected results appear in terms of improving liver diseases, especially for those with non-alcoholic fatty liver disease, but this solution is considered somewhat long-term [67]. However, liver damage resulting from excessive alcohol consumption is not one of their main priorities, and this affects their lives because of sleep difficulties, chronic insomnia, stress, and severe fatigue at times. To obtain better results, it is necessary to coordinate between many specialties in the field of health care, with the provision of complete medical teams consisting of doctors and paramedics specialized in each field, and to provide drug treatments and rehabilitation for these patients specifically designed with lifestyle interventions to maintain liver health. Among the specialties that must be available urgently are hepatologists to determine the state of the liver through regular tests for liver sclerosis, liver cirrhosis, and hepatocellular carcinoma, specialists in treating AUD, and other specialists such as social workers whose role is to prevent relapse through a careful study of the social and economic status of the case, and specialists in the field of therapeutic nutrition to treat metabolic disorders and muscle loss resulting from alcohol addiction to improve liver health [68].

Psychosocial therapy is the treatment that should be based on in the treatment of people with AUD and associated chronic liver disease. This can be done by organizing group therapy sessions for patients who have been able to overcome the problem of alcohol addiction, because the main goal of such sessions is to improve behavior. The encouragement of combining intensive medical care with integrated cognitive-behavioral therapy gives promising results [69]. Therefore, work should be done to develop integrated models and drug and behavioral plans that treat patients with liver health as their goal, considering metabolic dysfunction. These adjustments could also facilitate joint research endeavors to address knowledge gaps and potentially alleviate the worldwide burden of lifestyle-induced chronic liver disease [68].

4.3. Pharmacologic Medications for AUD

In the past, the FDA has agreed to three drugs for treating AUD in the following order: disulfiram, oral naltrexone, and an extended-release formulation of naltrexone. Contemporary approvals for treating AUD incorporate drugs as first-line treatments: naltrexone, acamprosate, and disulfiram. The treatment period alters from months to years according to the AUD severity and genetic polymorphism of the individual [70].

4.3.1. Naltrexone

Naltrexone is the first-line medication for AUD. It acts as an opioid receptor antagonist that declines alcohol desires. It inhibits the danger of returning to heavy consumption. Only dizziness and sleepiness have also been reported as Naltrexone adverse effects. The liver function test should be measuring monthly [71].

4.3.2. Acamprosate

Acamprosate, a crucial analog of gamma-aminobutyric acid (GABA), is thought to modify alcohol utilization by changing calcium channels, adjusting GABA transmission, and minimizing glutamate activity. These mixtures of mechanisms are believed to lower the positive reinforcement of alcohol abuse and reduce appetites during withdrawal [72]. Typically dose of the Acamprosate for adult two tablets every dose three times daily. Gastrointestinal symptoms and nervousness are the most common adverse effects of Acamprosate [71]. The AUD individuals with renal problems

should inform the physician. It is safe for hepatic patients, old persons, child, and breastfeeding mom [72].

4.3.3. Disulfiram

Disulfiram is first activated in the stomach and converted into diethyldithiocarbamic acid (DDC) in the bloodstream. DDC then undergoes phase II metabolism in the liver, producing S-oxidized compounds, which are the active metabolites responsible for disulfiram's therapeutic effects. These active metabolites compete with the NAD molecule at the cysteine residue in the active site of ADH, making disulfiram an irreversible inhibitor of ADH1. When taken at therapeutic doses, alcohol consumption leads to increased serum acetaldehyde, causing symptoms such as facial flushing, headache, vertigo, tachycardia, and sweating. This reaction, known as the Disulfiram-alcohol response, discourages alcohol consumption. The severity of this effect is dose-dependent for both disulfiram and alcohol. However, disulfiram does not directly address the neurobiological mechanisms of alcohol addiction [73].

Disulfiram is administered orally, with doses ranging from 250 mg to 500 mg once daily. Patients with AUD should avoid alcohol for at least 14 days after discontinuing disulfiram. Increasing the dose beyond 500 mg/day provides no additional benefit. A test dose of alcohol to provoke a disulfiram-alcohol reaction is no longer recommended. However, patients should be fully informed about the adverse effects of disulfiram when combined with alcohol before starting the treatment [70, 74].

Patients with AUD who have liver disease or heart failure should not be treated with Disulfiram, as it can exacerbate these conditions. In older patients, the starting dose should be lower. Disulfiram can cause both minor and major side effects. Minor side effects include seizures, psychiatric disturbances, optic neuritis, cardiac events, and hepatitis. Major side effects include insomnia, headache, and a metallic taste. Drug-drug interactions can be fatal, particularly when Disulfiram is combined with acetaminophen, omeprazole, phenytoin, imipramine, or any drugs that activate cytochrome P450 [73].

4.4. Promising Pharmacological Medications for AUD

Numerous medications such as topiramate, varenicline, gabapentin, and ondansetron have displayed promise in the management settings of AUD.

4.4.1. Topiramate

Topiramate, an anticonvulsant drug, is one of the most promising drugs for AUD based on its medium validity across various medical trials. One benefit of topiramate is its competence to be received while patients are still drinking alcohol, making it a potential therapy for starting abstinence or reducing impairment. However, it has probable negative effects, specifically those involving cognition and memory, requiring slow dose uptake and careful monitoring. Investigations advocate a pharmacogenetic strategy may improve the effectiveness, acceptability, and security of topiramate. Zonisamide is another anticonvulsant drug. It is like the topiramate mechanism of action but with a better safety profile [1].

4.4.2. Varenicline

Varenicline, a nicotinic acetylcholine receptor incomplete agonist accepted for smoking cessation, has shown possible in regards to AUD. Several studies favor its ability, remarkably in heavy-drinking smokers [75].

4.4.3. Ondansetron

Ondansetron, a 5-HT3 antagonist largely treated as an anti-nausea medicine, has been assessed for its prospective function in AUD therapy. Documents have confirmed its efficacy through a pharmacogenetic policy, and decisions propose it may be favorable for populations with limited

genetic modifications in the genes encoding the serotonin transporter (5-HTT) and the 5-HT3 receptor. Although not universally efficient, ondansetron has shown promise for certain subgroups within the AUD individuals [76].

4.4.4. Gabapentin

Gabapentin, submitted as a second-line treatment for AUD. It acts as a GABA analog, decreases excitatory neurotransmission, and impacts the neurological alterations associated with alcohol. Frequent adverse consequences involve insomnia, headaches, and vertigo. For AUD, gabapentin is usually initiated at 300 mg/day (especially in patients with cirrhosis), with regular increases of 300 mg every 1–2 days depending on the patient's reaction and acceptability, aspiring for an objective dosage of 600 mg administered three times daily [70].

5. Future directions

Pharmacological improvements in the management of AUD are promising, with drugs such as topiramate, varenicline, and ondansetron demonstrating excellent potential. Continued research, with a particular focus on individualized medication and pharmacogenetics, is necessary to progress treatment outcomes. In addition, the integration of digital tools such as apps, artificial intelligence, and telemedicine supports new prospects to monitor, treat, and support patients with AUD, particularly in remote areas. A patient-centered, multidisciplinary approach implying hepatologists, addiction specialists, psychologists, and social workers is essential to addressing AUD and its impact on liver health. Future research should prioritize the development of integrated treatment models that combine medical, behavioral, and lifestyle interventions. Furthermore, collaborative research across disciplines and institutions will be vital in bridging gaps in understanding the development of AUD and developing comprehensive strategies aimed at treating AUD and preventing alcohol-related liver disease [77].

6. Rehabilitation

"Rehabilitation, the subsequent stage of recovery, commences following the subsiding of withdrawal symptoms [78]. Its objectives align with those of any persistent, recurring disorder: maintaining motivation, altering perspectives on recovery, and ultimately minimizing the likelihood of relapse. The prevention of relapse among older adults with alcohol use disorder is particularly imperative, given that their outcomes, in certain instances, are at least equivalent and, in some cases, superior to those of younger individuals." [79]. Research indicates that a significant proportion of older adults receiving treatment for AUD maintain abstinence for an extended period. To enhance long-term sobriety, a comprehensive approach incorporating pharmacological interventions, psychological support, and social-behavioral strategies is essential [21]. However, The development of a comprehensive rehabilitation plan necessitates interdisciplinary collaboration to assess resource availability, transportation logistics, eligibility criteria, insurance coverage, community support network, and familial involvement. Prioritizing patient preferences is essential. A tailored treatment regimen for substance abuse should be implemented in accordance with individual circumstances and Medicare regulations for both inpatient and outpatient services. Treatment modalities may involve intensive inpatient programs, day treatment, outpatient therapy, or community-based groups. Therapeutic interventions can include personalized assessment and feedback, cognitive-behavioral therapy, goal setting, and self-monitoring of consumption through journaling [81]. "Support groups and brief intervention are two of the most commonly used and successful methods for addressing various health issues." [82].

7. Mutual-help Groups

Mutual-help groups (MHGs) offer a valuable support system for older adults recovering from AUD. These peer-led groups provide a safe space for individuals to openly discuss their challenges, build supportive relationships, and develop relapse prevention strategies. By fostering a sense of community and shared understanding, MHGs can play a crucial role in facilitating long-term recovery [78]. Both MHGs are readily available and applicable to individuals seeking recovery from alcohol addiction [83, 84]. Among these programs, Alcoholics Anonymous (AA) holds the highest recognition. AA adopts a 12-step framework that centers on transforming perspectives and behaviors, conceiving and constructing a life free from alcohol, pinpointing circumstances that elevate the likelihood of relapse, and reinstating sobriety in the event of a return to heavy drinking [78]. "In numerous regions, community-based or outpatient Alcoholics Anonymous (AA) meetings are accessible on a frequent basis, often daily or more frequently. Moreover, many AA meetings are now conducted online. Participation in AA meetings does not necessitate insurance approval. MHGs are also a vital component of intensive inpatient care. Whether employed as supplementary therapy or as a core element of the treatment plan, the 12-step facilitation approach has demonstrated its effectiveness in enhancing the likelihood of positive outcomes across various treatment settings." [78]. The study suggests that 12-step programs are more effective than other interventions in promoting abstinence and reducing mental health service utilization among individuals with substance abuse issues. This results in significant cost savings for healthcare providers. While specialized 12-step groups exist to address specific needs, such as depression or gender-specific concerns, there is a concern that traditional MHGs may not be optimally suited for older adults. Older individuals, particularly those who have retired, may face unique challenges in MHGs due to differences in life experiences and perspectives. Age-specific counseling groups can offer a more conducive environment for open dialogue among individuals facing similar life challenges. By catering to the unique experiences and perspectives of older adults in recovery, these groups can foster a strong sense of community and support. The shared values, life situations, and goals within age- specific groups can facilitate the development of practical strategies and peer support, ultimately contributing to sustained sobriety [84].

8. Challenges facing treatment of alcohol use disorder

8.1. Treatment Gap

"The treatment gap for AUD in the United States is significant. Despite a large number of individuals requiring professional help, only a small percentage receive any form of treatment, whether behavioral or medical, within a year." [85]. The low rate of FDA-approved medication utilization for AUD in 2019 was primarily attributed to a lack of knowledge, screening, referral, treatment facilities, and societal stigma [86]. Misconceptions about treatment options, such as the belief in solely 28-day inpatient rehabilitation or abstinence-based programs, contributed to this gap. Additionally, a lack of understanding regarding standard drink definitions, dietary guidelines for moderate drinking, and the efficacy of FDA-approved medications further hindered treatment uptake. Educating the public about these issues, including defining a standard drink, is crucial for promoting healthier drinking habits and encouraging the use of effective treatment options [87]. Early identification and intervention are crucial in addressing alcohol use disorder (AUD) due to many people's unawareness of their own problematic drinking patterns. The Screening, Brief Intervention, and Referral to Treatment (SBIRT) model is an effective approach for detecting and intervening with individuals at risk of developing AUD in primary care settings [88]. This model requires minimal effort from healthcare providers and can also help identify other potential health issues. Despite its effectiveness, the SBIRT model is underutilized, with low rates of advice and referral for those with severe AUD. This emphasizes the need for greater implementation of AUD treatment in primary care settings [89].

Brief interventions have proven to be effective in curbing alcohol consumption among both men and women over a one- year period when compared to control groups [90]. However, if follow-up evaluations indicate that these interventions have not yielded the desired results, it is essential to transition to evidence-based pharmacological and behavioral treatments for alcohol use disorder. The treatment gap for addiction and psychiatric disorders in the United States is exacerbated by a shortage of specialized treatment facilities [91]. Outpatient treatment often falls short, necessitating a greater number of inpatient hospital beds to address the needs of those struggling with these conditions [92].

8.2. Challenges for Medication Development

The process of developing new medications for AUD is lengthy and complex. It can take decades to identify potential treatment targets and bring a drug to market. For instance, naltrexone, a medication used to treat AUD, was initially studied in animal models in the 1980s but wasn't approved by the FDA until 1995 [93]. The FDA approval process involves several stages. First, researchers identify potential drug candidates by examining their interactions with the brain's neurofunctional systems involved in AUD. They then study the drug's pharmacokinetics, effectiveness in animal models, and initial toxicity. Next, they conduct extensive toxicity testing both in vitro and in vivo to assess the potential for serious side effects.

"Following encouraging results in preclinical studies, a novel therapeutic agent undergoes rigorous clinical evaluation. Phase I trials primarily focus on assessing the safety and tolerability of the drug in healthy volunteers. Subsequent Phase II trials involve patients with AUD to evaluate efficacy and identify potential adverse effects. Phase III trials further validate the drug's efficacy and safety in larger patient populations. Upon completion of these phases, the drug developer submits a new drug application (NDA) to the regulatory authority, such as the FDA. The regulatory body meticulously reviews the comprehensive data from preclinical and clinical studies. If the NDA is approved, the drug may be marketed for the treatment of AUD." [93, 94].

8.2.1. Pharmaceutical Industry Commitment

The addiction pharmacotherapy clinical pipeline has seen a 34% increase in the past five years, with 29 programs in 2018 rising to 39 in 2022 and 9 in 2023 from 8 in 2019 [95]. However, this growth pales in comparison to other major diseases and disorders, with only one new chemical entity, lofexidine for opioid use disorder, approved by the FDA in the past five years. This lack of novel chemical entities in the clinical pipeline is one of the factors contributing to industry's lack of funding for addiction pharmacotherapy development [95, 96].

8.2.2. Stigma

"The language used to describe individuals with alcohol use disorder (AUD) significantly impacts the societal stigma surrounding this condition. Comparative studies across multiple nations demonstrate that individuals with AUD are more frequently perceived as personally responsible for their affliction than those diagnosed with other mental health disorders or cognitive impairments [97]. Furthermore, the perceived stigma associated with AUD can influence an individual's willingness to seek professional mental health treatment." [98]. CLOSING THE TREATMENTGAP: NEW SOLUTIONS FOR THE TREATMENT OF ALCOHOL USE DISORDER

Given the complex interplay of biological factors contributing to AUD, a wider range of therapeutic approaches is necessary. While some individuals may benefit from interventions targeting cravings or impulsivity, others may respond better to treatments addressing withdrawal symptoms or the lingering negative emotional states associated with protracted withdrawal. Similar to other medical conditions, individuals with AUD should have access to a variety of treatment options. Researchers are actively exploring the development of a more comprehensive

therapeutic arsenal that can be tailored to individual patient needs [92].

8.3.1 Educating the Public

A growing body of literature is accessible to the general population, providing insights into the characteristics of unhealthy alcohol consumption, individual susceptibility to alcohol-related pathologies, and available treatment modalities for alcohol misuse and alcohol use disorder [4].

8.3.2 Broadening End Points for the Approval of Medications for the Treatment of Alcohol Use Disorder

The Food and Drug Administration (FDA) recognizes that reducing alcohol consumption can have significant clinical benefits for individuals with AUD. They accept abstinence and a reduction in heavy drinking days as primary outcomes for Phase III clinical trials evaluating new medications for AUD treatment. Four or more drinks for women and five or more for males in a single day is considered a heavy drinking day [100].

However, studies have demonstrated that even more modest reductions in alcohol consumption, as measured by the World Health Organization (WHO) risk levels, can also lead to clinically meaningful improvements. These reductions are associated with a decrease in alcohol-related consequences and positive changes in mental health. The WHO risk levels categorize alcohol consumption based on the amount consumed per day, with low, medium, high, and very high risk levels defined for both men and women [101].

Therefore, while abstinence and significant reductions in heavy drinking days are important goals, achieving even lower levels of alcohol consumption can still provide substantial benefits for individuals with AUD [102].

Secondary analyses of AUD pharmacotherapy trials demonstrated that reductions in WHO drinking risk levels were as effective as or more so than FDA-approved measures in assessing treatment efficacy. Furthermore, these reductions were sustained post-treatment and correlated with improved functioning. These findings suggest that WHO risk level reductions could serve as valuable outcome indicators in Phase III clinical trials, potentially incentivizing pharmaceutical companies to invest in AUD medication development [103, 104].

8.3.3 Engaging Screening, Brief Intervention, and Referral to Treatment

As noted above, the research indicates that implementing screening and brief intervention strategies within primary care settings is a cost-effective approach to reducing alcohol consumption and mitigating associated health risks. Studies have consistently demonstrated the efficacy of these interventions in curbing alcohol misuse and preventing the development of alcohol-related pathologies [105-107].

The USPSTF recommends employing the Alcohol Use Disorders Identification Test–Consumption (AUDIT-C) for screening adult patients for alcohol use disorders [88]. Additionally, the NIAAA single alcohol screening question, which inquires about the frequency of excessive drinking episodes, is another effective screening tool [88]. Brief interventions in healthcare settings and primary care visits involve providing patients with personalized feedback regarding their alcohol consumption patterns, identifying high-risk drinking behaviors, offering clear guidance on reducing alcohol intake, and establishing a plan to decrease consumption [108].

For individuals exhibiting significant alcohol problems or moderate to severe alcohol use disorders, more intensive therapeutic interventions are necessary. These interventions should be delivered by licensed therapists specializing in addiction and may include the use of FDA-approved medications for alcohol use disorders, which can be administered in primary care settings or by addiction-specialist physicians. Referral to specialized treatment programs is often indicated for such cases [109].

8.3.4. Addressing Stigma

The use of stigmatizing language, such as "alcohol abuser," when referring to individuals with AUDs can have negative consequences for both patients and clinicians. By adopting more neutral and compassionate terminology, like "person with an alcohol use disorder," clinicians can foster a more positive and supportive therapeutic environment. This shift in language can help reduce stigma, mitigate feelings of shame and guilt, increase the likelihood of seeking treatment, and promote the belief in recovery [95, 110]. Furthermore, using terms like "alcohol-associated liver disease" instead of "alcoholic liver disease" can minimize the moral implications associated with alcohol-related health problems [110, 111].

Conclusion

Alcohol Use Disorder (AUD) is a severe health condition primarily affecting the liver, which is the first organ to process alcohol. Treatment requires a multidisciplinary approach involving medical, psychological, and social strategies. Despite medications like naltrexone, acamprosate, and disulfiram showing promise in reducing cravings and preventing relapse, liver damage remains a major concern. Emerging biomarkers offer new insights into alcohol consumption patterns, aiding in diagnosis and monitoring. Despite the availability of effective treatments, a significant treatment gap persists. To address this, a multi-faceted approach is needed, including expanding treatment options, increasing screening and intervention efforts, reducing stigma, and implementing a more comprehensive definition of recovery. A heuristic framework for AUD can guide treatment development, focusing on binge/intoxication, withdrawal/negative affect, and preoccupation/anticipation stages. Tailored assessment and intervention strategies can enhance treatment efficacy, addressing the specific needs of diverse populations, including older adults. Public education and awareness campaigns are crucial for reducing stigma and promoting understanding of AUD's consequences.

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Consent to publish

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