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REVIEW

Neurobiology and the Treatment of Alcohol Use Disorder: A Review of the Evidence Base

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Abstract: Alcohol use disorder (AUD) is a significant public health concern, accounting for a majority of substance use disorder cases in the United States. Treatment for AUD is complex, with multiple intervention points that may be further complicated by genotype and phenotype, resulting in diverse outcomes. In order to better understand the current landscape of AUD treatment, the present review considers different etiological models of AUD and assesses the evidence base of current treatment options. The first section of this review summarizes various etiological models of AUD and presents different approaches to classifying the disorder. Various theories, including neurobiological models, are discussed. The second section presents a comprehensive analysis of available treatment options for AUD, encompassing behavioral and pharmacological interventions and their current evidence base. Finally, this review discusses the ongoing treatment gap and significant factors contributing to low treatment utilization. Together, this review provides an overview of different etiological processes and mechanisms of AUD, as well as summarizes the literature on key treatment approaches. By integrating historical, theoretical, and empirical data, this review aims to inform both researchers and providers with valuable insights to advance AUD treatment approaches and narrow the treatment gap.

Keywords: alcohol use disorder, AUD treatment, substance use disorder, neurobiological models, treatment gap

Introduction

Alcohol use disorder (AUD) is one of the most common psychiatric disorders and represents a serious health condition, affecting nearly 14.1 million people in the United States alone.[1] It is estimated that alcohol contributes to 1 in 10 adult deaths in the United States and more than 140,000 Americans die from alcohol-related causes annually, making it a leading risk factor for premature death.[2] Worldwide, the harmful use of alcohol causes approximately 3.0 million deaths every year and accounts for 5.1% of the total global burden of disease.[3] Higher doses of alcohol in the brain (ie, blood alcohol level 0.08%–0.15%) can lead to motor impairment, muscular incoordination, impairments in reaction time, impairments in judgment, impairments in sensory processing, and impairments in cognitive function. Heavy drinking, both continuous and episodic, has been linked to over 200 diseases and injuries.[4,5] Even at low doses, alcohol consumption has been linked to health and cancer risks.[6] Within mental health and medical settings, it is estimated that at least 25% of clients are likely to have AUD as part of their presenting problem and AUD is highly comorbid with other psychiatric conditions such as depression, anxiety disorders, and post-traumatic stress disorder.[7–9]

Despite its prevalence and consequences, treatment-seeking rates for AUD are surprisingly low.[10,11] It is estimated that less than 10% of individuals that meet criteria for current AUD will seek treatment.[12–14] Treatment seeking status is indicated by a desire to enter treatment and does not necessarily indicate that these individuals will receive treatment. Epidemiological data suggest that there is an average lag of 8 years between AUD onset and the decision to seek treatment.[15] Individual- and systemic-level barriers, coupled with the perceptions around natural recovery and the need for treatment, likely impact treatment utilization. Together, the high documented rates of AUD and observed consequences on health demand research attention in order to improve the landscape of AUD treatment.

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The Etiology of AUD and Current Diagnostic Practices

To develop effective therapeutic agents for such a complex disorder, it is important to understand the mechanisms related to the development and maintenance of AUD. The NIAAA currently defines AUD as a "chronic relapsing brain disease characterized by an impaired ability to stop or control alcohol use".[16] Neurobiological models of AUD theorize that alcohol addiction is based on pathological changes to the system produced by chronic alcohol use.[17,18] The allostatic model of addiction[19,20] emphasizes three primary stages, which are thought to cycle among one another and increase in amplitude with repeated experience. The first stage is characterized as "binge/intoxication", or loss-of-control drinking. Alcohol activates the reward circuitry of the brain (eg, neurocircuitry in ventral striatum), leading to acute reinforcing effects and increased salience of alcohol cues (ie, incentive salience). The positive reinforcing effects of alcohol are also facilitated at the neurotransmitter level by dopamine, opioid peptides, and γ-aminobutyric acid (GABA). As the dose of alcohol increases, activation in the basal ganglia shifts from the nucleus accumbens to the dorsal striatum, engaging "habit" neurocircuitry (ie, habit formation). In the "withdrawal/negative affect" stage, withdrawal from chronic alcohol use disrupts reward neurotransmitter function (eg, dopamine and opioid peptide function in nucleus accumbens), creating a reward deficit. Further, changes to key neuromodulators of stress reactivity (eg, neuropeptide Y and corticotropin-releasing factor (CRF)) enhance stress reactivity in the amygdala. Excessive drinking at this stage is thought to be maintained by negative reinforcement (ie, drinking to alleviate negative affective and physiological states). Finally, the "preoccupation/anticipation stage" involves adaptations to the prefrontal cortex (ie, the control center of the brain) and is characterized by the return to alcohol-seeking behaviors after a period of abstinence. These alcohol-seeking behaviors are encouraged by prolonged deficits in reward circuitry (ie, dopamine, opioid peptide, and GABA function) and protracted stress effects (eg, corticotropin-releasing factor, norepinephrine, neuroimmune function, neuropeptide Y, and oxytocin). Essentially, AUD is theorized to be the result of deficits in both cognitive control and reward circuitry.[21] Understanding the neurobiological bases behind an individual's inability to control behavior toward alcohol and increased sensitivity to the saliency of alcohol cues helps to explain why individuals with AUD continue to struggle in controlling their drinking, despite the desire to quit or cut down. This model offers advantages for outlining neural mechanisms relevant to treatment research and shifting the perspective of AUD away from a "lack of willpower." However, the neuroscience framework is not the only perspective with valuable implications for clinical translation and only represents a piece of the puzzle.

The biological mechanisms discussed above fit within a larger framework known as the biopsychosocial model of addiction.[22,23] This model, recently reviewed and updated by Ray and Grodin,[24] is meant to provide a rich multidimensional perspective that addresses the complexity of the disorder and emphasizes the interplay of multiple factors, rather than relying on a single explanatory factor. Support for this model has been shown through work on the interplay of genetics and environment, impacting one's susceptibility towards AUD.[25,26] The psychosocial components of the model include psychological theories and social influences, with both domains lending significant discoveries for treatment development. Psychological models of addiction stress the importance of factors such as reinforcement-based learning, subjective response to alcohol, maladaptive cognitive processes, personality factors (eg, impulsivity), and developmental psychopathology.[27] Social models of addiction investigate factors such as social networks, parent modeling, social identity, and sociocultural context. Taken together, a biopsychosocial approach to alcohol use disorder provides an array of etiological processes and mechanisms for clinicians to consider in the treatment of AUD. Additionally, it can offer rationale towards collaboration between professionals (eg, physicians and psychologists) and more comprehensive care targeting multiple domains of functioning such as work, health, and interpersonal relationships.

As theorized by contemporary models of addiction, each individual develops an AUD based on the complex interaction of underlying genetic and environmental mechanisms.[28] Some of the strongest support for this model is shown through twin and adoption studies.[29–31] Further, recent models theorize that AUD manifests itself in a continuum of severity and phenotypic profiles, ranging from the occasional social drinker to the chronic relapsing heavy drinker. As opposed to a disease model orientation (ie, defined by presence or absence), conceptualizing AUD as existing on a continuum of severity may aid in greater problem recognition among lower severity individuals. Further, research on the prevention paradox confirms that a majority of the overall harm caused by alcohol arises from the large majority of individuals who drink at the light to moderate level, as opposed to the small minority at the severe end. Therefore, it can be suggested that greater health improvements at the population level will come from prevention strategies aimed at the entire population of drinkers. While there is some concern

over how the continuum model of severity will affect the treatment landscape, advancing this model may have significant benefits to public beliefs about the nature of alcohol use and potentially improve overall population-level outcomes. Support for these models, including consumption-based models that define AUD in terms of heavy use over time,[32] can be seen through efforts to promote drinking reduction as a viable treatment target. For example, WHO drinking risk levels have been shown to correspond to improvements in health and quality of life and have been suggested as clinically meaningful endpoints to be used in clinical trials.[33]

Research has acknowledged the heterogeneity of AUD and attempted to capture different phenotypic profiles through empirically based typology systems that consider multiple factors such as genetics, drinking profiles, motivation for drinking, and personality traits (eg,[34–38]). However, a crucial limitation to the translation of addiction research into clinical samples lies in the misalignment between research-based models of AUD and the current DSM diagnostic criteria. A major critique of the DSM-5's AUD criteria is that they are not informative about underlying mechanisms of dysfunction and fail to account for the heterogeneity that exists. If research has given us empirical data to support a wide array of mechanisms involved in the development and maintenance of AUD and identified important phenotypic profiles related to treatment outcomes, should our diagnostic methods not be able to reflect and accurately capture these mechanisms?

Currently, the diagnosis of AUD is set to represent a single disorder, ranging along three categories of severity (DSM-5®;[39]). To be diagnosed with AUD, an individual must meet at least two of 11 criteria. The 11 diagnostic criteria include (1) drinking larger amounts of alcohol or drinking over longer periods than planned; (2) having the desire to or attempting to cut down or stop without success; (3) spending considerable time drinking alcohol and recovering from its effects; (4) experiencing a persistent craving for alcohol; (5) failing to fulfill major social role obligations, such as those related to work, home, or school; (6) neglect of other activities; (7) continuing to drink despite the fact that drinking is causing social or interpersonal problems; (8) continuing to use despite knowing that alcohol is causing recurrent physical or psychological problems; (9) drinking repeatedly in a way that that has the potential to create physical harm (eg, drinking and driving); (10) exhibiting signs of physical tolerance; and (11) showing signs of physical withdrawal. Based on the number of criteria met, the AUD is then classified as mild (two to three symptoms), moderate (four to five symptoms), or severe (six to 11 symptoms).

The new conceptualization of AUD in DSM-5 marks a change from the previous edition of the DSM (ie, DSM-IV), which discriminated between alcohol abuse and alcohol dependence. Additionally, the new criteria eliminated the previous DSM-IV symptom of "repeated alcohol-related legal consequences", and added a criterion for craving. The problem with this approach is it oversimplifies the phenotypic profile of individuals with AUD and lumps them into three categories based on a simplified "count" of symptoms. There are over 2000 different symptom profiles possible to meet criteria for AUD, including approximately 55+ ways to configure a "mild" diagnosis, 330+ ways to configure "moderate", and 462+ ways to configure a "severe" diagnosis. By the terms of the current diagnostic system, an individual presenting with withdrawal symptoms, cravings, and tolerance would be labeled the same as an individual presenting with interpersonal problems and a persistent desire to control their drinking. The DSM is often used to determine treatment programs, despite the fact that the thresholds set by the DSM have often failed to predict treatment response.[40–42] Further, the DSM is often used to determine study inclusion for clinical trials in order to promote external validity, despite the fact that use of the DSM likely limits the enrollment of individuals representing the larger spectrum of functioning. Overreliance on the categorical classifications set by the DSM may present a serious hindrance to the translation and reverse-translation between research findings and clinical decision-making.

To address this issue, there has been a movement toward a new classification framework known as the Research Domain Criteria (RDoC), an initiative funded by the National Institute of Mental Health (NIMH) in 2009. RDoC is intended to be a transdiagnostic, neuroscience-based research framework approach that focuses on specific domains that can help explain psychopathology in terms of varying degrees of dysfunction in fundamental psychology/biological systems.[43,44] RDoC is not meant to serve as a diagnostic guide, although it is hoped that research using the RDoC framework can lead to revisions to diagnostic systems, as well as the development of screening tools and treatment interventions. To represent RDoC in the addiction field, the Addictions Neuroclinical Assessment (ANA) was recently proposed as a research framework for neuroscience-informed assessment that captures three functional domains – incentive salience, negative emotionality, and executive dysfunction.[45,46] This framework aims to understand the heterogeneity in AUD by leveraging deep phenotyping profiles coupled with factor analytic methods.[47,48] The benefit of these research methods over DSM is that they do not rely on disorder-based categories and

instead span functional domains, each containing a set of constructs that include elements, processes, mechanisms, and responses informed by various types of information including genetics, brain circuitry, behavior, physiology, and self-report. Once validated, the heuristic framework offered in ANA presents new opportunities whereby dysfunctions in these domains may serve as treatment targets.

In addition to the ANA framework as a translational approach, understanding reward and relief drinking has been advanced in recent years as a clinically relevant marker. These two subtypes of AUD are centered around the underlying motivation for alcohol consumption, specifically categorized as drinking for hedonic pleasure (reward type) or drinking to mitigate negative emotions (relief type). Recent empirical studies have underscored the potential clinical relevance of this typology by demonstrating that individuals exhibiting reward drinking benefit more from naltrexone, a medication known to blunt the rewarding effects of alcohol, compared to other medications.[49,50] The identification and differentiation of reward and relief drinking subtypes within the context of AUD may offer valuable insight into tailoring personalized treatment interventions.

By acknowledging AUD as a complex clinical phenomenon, we must inherently accept that there is not a single causal path to this disorder. By creating a translational framework that integrates neurobiological models of addiction with observed clinical phenotypes, we can refine our conceptualization of clinical phenomena and make more precise treatment selection.

Overview of AUD Treatment Options

According to NESARC-III data, which uses AUDADIS, among those with current, past 12-month AUD diagnoses, the most commonly reported treatment modalities included 12-step programs (4.5%), health-care providers (3.6%), outpatient substance abuse treatment (2.0%), emergency departments (1.4%), various family and social services (1.4%), inpatient detoxification (1.3%), and other inpatient programs (1.2%).[51] The available treatment options will be briefly reviewed in two broad categories: behavioral treatments and pharmacological treatments.

Behavioral treatment options for AUD include cognitive-behavioral therapy, motivational interviewing, inpatient and outpatient rehabilitation facilities, and mutual support/12-step groups. Among the behavioral treatments with the best support are brief interventions, motivational interviewing, cognitive-behavioral treatment, 12-step facilitation treatment, behavioral couple therapy, cue exposure treatment, mindfulness-based relapse prevention, and the community reinforcement approach. Figure 1 offers a visual representation of common psychosocial treatments, ranked by AUD disorder stage and strength of evidence base.[52]

Although often underutilized, pharmacological treatment options do exist. Since 1949, the United States FDA has approved 3 evidence-based medications for treating AUD. These pharmacotherapies include 1) disulfiram (Antabuse), first introduced in 1951; 2) naltrexone, approved in 1994 as an oral formulation (Revia) and in 2006 as a long-acting injectable formulation (Vivitrol); and 3) acamprosate (Campral), approved in 2004.[53] Disulfiram is an aversion therapy agent that blocks the enzyme aldehyde dehydrogenase and leads to the build-up of acetaldehyde causing facial flushing, headache, hypotension, nausea, and vomiting. Naltrexone works by blocking the endogenous opioid system and decreasing the craving for alcohol, as well as blunting the rewarding effects of alcohol. Finally, acamprosate works by increasing gamma-aminobutyric acid (GABA) and decreasing *N*-methyl-D-aspartate (NMDA) in order to reduce craving for alcohol and lessen negative emotional states during withdrawal. Overall, these medications target symptomatic improvement (eg, suppression of alcohol-craving) or act to blunt or punish the reinforcing properties of alcohol.

While the number of approved medications for AUD pales in comparison to other psychiatric disorders such as major depression, which shares a similar prevalence with AUD yet boasts more than 20 medications approved by the FDA, there has been progress in medication development in the past few decades. Figure 2 highlights the current repertoire of promising medications, stratified by the strength of evidence base and appropriate AUD disorder stage.[52] Currently, there are several off-label (ie, not FDA-approved for the treatment of AUD) medications with promising findings, including nalmefene, baclofen, gabapentin, ondansetron, topiramate, varenicline, ABT-436, and zonisamide (Litten et al, 2016, Ray et al, 2019). Additionally, other off-label medications with preliminary support include Mifepristone (RU-486); Aripiprazole; Ibudilast; Prazosin; Doxazosin; *N*-Acetylcysteine (NAC); and Suvorexant. There are also novel medications with promising theoretical support, including: *N*-[(4-Trifluoromethyl) benzyl] 4-methoxybutyramide (GET73), ASP8062, PF-5190457, and cannabidiol (CBD).

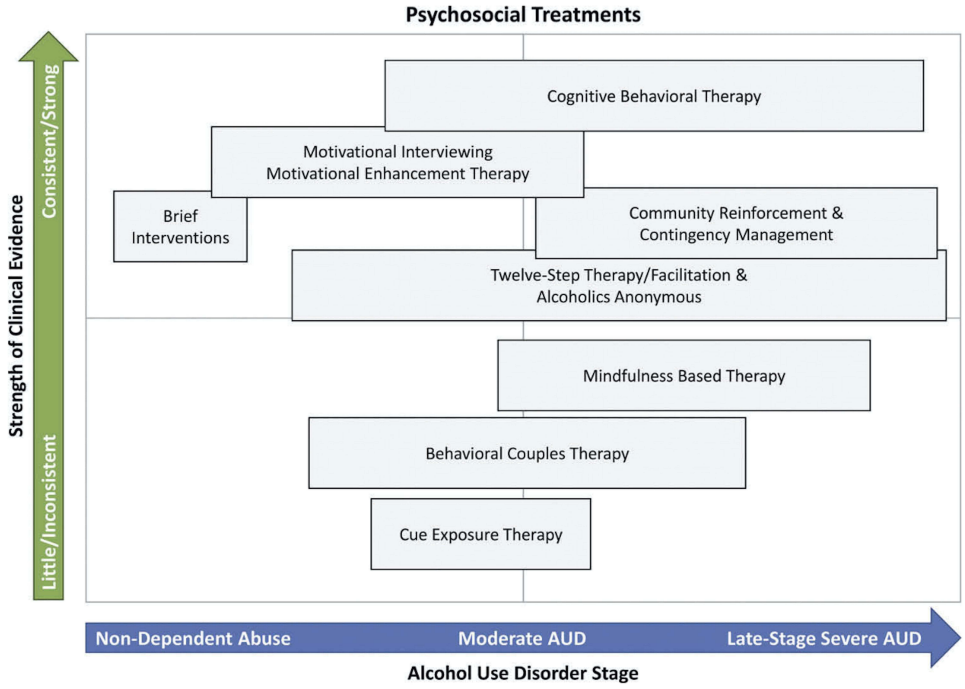

Figure 1 Summary of available psychological treatments for AUD with the y-axis indicating the strength of the evidence in favor of a particular treatment and the x-axis indicating the recommended placement of that treatment across the continuum of AUD severity.
Notes: Reprinted from Ray LA, Bujarski S, Grodin E et al. State-of-the-art behavioral and pharmacological treatments for alcohol use disorder. *The American Journal of Drug and Alcohol Abuse*. 2019;45(2):124–140.[52]

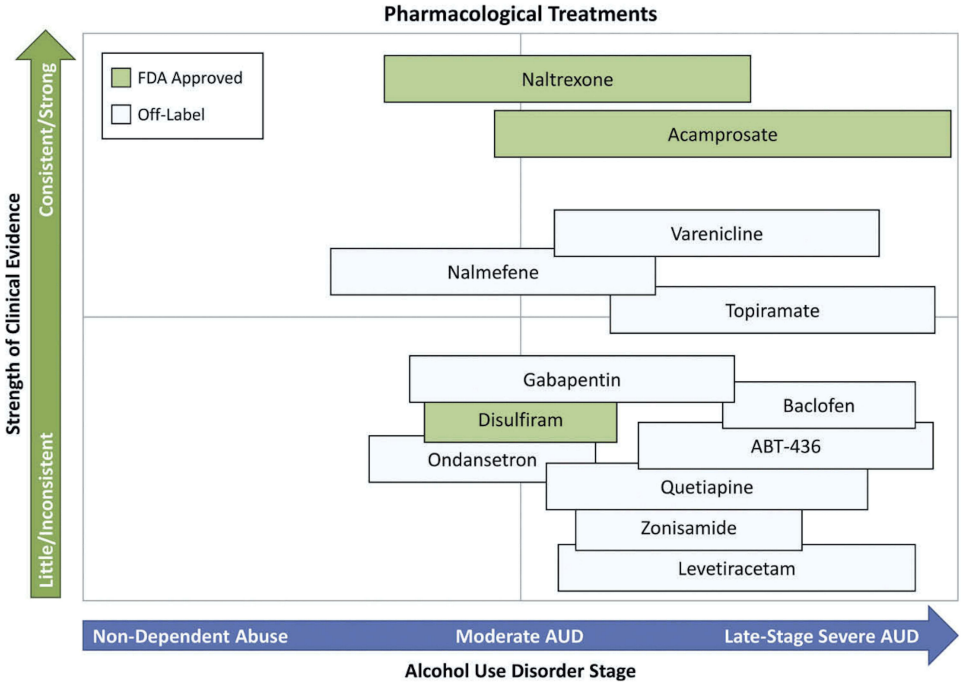

Figure 2 Summary of available pharmacological treatments for AUD with the y-axis indicating the strength of the evidence in favor of a particular treatment and the x-axis indicating the recommended placement of that treatment across the continuum of AUD severity. Pharmacotherapies are divided into FDA-approved and off-label treatments.
Notes: Reprinted from Ray LA, Bujarski S, Grodin E et al. State-of-the-art behavioral and pharmacological treatments for alcohol use disorder. *The American Journal of Drug and Alcohol Abuse*. 2019;45(2):124–140.[52]

Given the importance of translating research findings into clinical settings and the potential burden placed on providers to stay up to date on the most recent clinical trial results, comprehensive summaries on the evidence-base for available treatment methods are routinely published to inform best treatment practices (eg,[52,54–56]). Most recently, the American Psychiatric Association published "Practice Guideline for the Pharmacological Treatment of Patients with Alcohol Use Disorder",[57] which translates current findings on AUD pharmacotherapies into evidence-based recommendations for medication use. It also includes a discussion on factors relevant to medication success (eg, non-compliance, negative drug interactions, and bothersome side effects) and recommendations.

The combination of multiple therapeutic approaches (eg, behavioral and pharmacological) has also been investigated as a potential treatment approach and reviewed in the literature.[58–60] For example, meta-analytic approaches have been used to investigate the effectiveness of combined interventions compared to monotherapy in the treatment of AUD. Most found a benefit in incorporating pharmacotherapy with psychotherapy, as compared to psychotherapy alone[61–63]. However, this pattern of benefit was not found in the landmark US study Project COMBINE.[64] The results of adding psychotherapy to pharmacotherapy treatment are also unclear, with fewer studies demonstrating a possible added value for combined therapy.[61] Other studies have also investigated the benefits of combining multiple psychosocial approaches, such as cognitive-behavioral therapy, motivational interviewing, and multiple pharmacotherapies. In a previous meta-analysis,[62] CBT combined with another psychosocial treatment (ie, motivational interviewing or contingency management) showed a pooled effect size roughly double that of studies testing CBT alone. The literature on combining multiple pharmacological options is difficult to summarize succinctly given differences in co-morbidities, medications, and treatment targets. A systematic review investigating the clinical evidence of combined pharmacological interventions for individuals with AUD without co-morbid conditions found no significant benefit of combination medication over single agents.[59] Further research in the area of combination therapies is warranted in order to clarify the utility of this approach.

Of note, there has been some progress in developing novel treatment options beyond the domains of current behavioral and pharmacological treatment options. One such treatment option is repetitive transcranial magnetic stimulation (rTMS), a non-invasive neurophysiological tool that has the ability to modulate activity in discrete brain regions and has shown therapeutic efficacy in major depression[65,66] and tobacco use disorder.[67,68] Given the association of brain reward circuitry with alcohol use disorder, stimulation of these neutral systems, such as the dorsal lateral prefrontal cortex (dIPFC), via rTMS may serve as a useful treatment for AUD.

Another innovative approach to the treatment of AUD is technology-based interventions. For example, telemedicine programs that can be accessed through one's smartphone have shown promise for reducing alcohol use.[69] Other technology-based interventions that have shown preliminary evidence for targeting alcohol consumption include web-based applications (eg,[70] wearable biosensors,[71] smartphone applications (eg,[72] and computer-delivered treatment modules.[73,74] Notably, systematic reviews and meta-analyses of technology-based interventions have highlighted limitations on the research support of these interventions, including small effect sizes and limited well-controlled comparisons.[75–77] However, the availability of these interventions is promising, as they reflect a push in the field for innovative treatment options that can improve accessibility and help bridge the alarming "treatment gap" that exists.

Within AUD treatment research, there is a well-documented "treatment gap."[10,78,79] This "gap" may be impacted by factors affecting individuals' motivation to seek treatment, as well as factors affecting individuals' ability to connect with care. In a recent review by our laboratory,[10] we have discussed various reasons for low treatment seeking rates, including both person-related treatment barriers and treatment-related barriers. Person-related barriers that were identified in the review include attitudes and beliefs (eg, "my drinking isn't serious enough" and "the problem will get better by itself"), fear of stigma, and socioeconomic status. The treatment-related barriers included "lack of treatment knowledge and options" and "cost of treatment"[10] For treatment utilization, the latest national surveys estimate that less than 8% of adults with AUD receive pharmacotherapy and/or psychotherapy treatment.[1,78,80] Globally, it is estimated that approximately one in six people with AUD receives treatment.[79] These treatment statistics are even lower when confined to pharmacotherapy utilization. In the United States, it is estimated that only 4% of individuals with AUD receive a Food and Drug Administration (FDA)–approved medication for treatment.[81–83] Recent results from the 2019 National Survey on Drug Use and Health indicate that this rate may be as low as 1.6%.[84] It should be noted that these rates are confined to utilization of FDA-approved medications and there is some evidence that these rates are slightly higher when off-label medications are taken into consideration.[85,86]

The low rates of medication utilization for AUD may be due to the small-to-moderate effect size of the available medications, further complicated by factors such as non-compliance, co-morbid conditions, and genetic variations impacting response. Data-driven methods, such as machine learning, offer unique opportunities to identify factors affecting treatment response. For example, the first genome-wide association study of AUD treatment outcomes found evidence of a polygenic effect on AUD treatment response and identified certain genetic variants shown to influence medication effects.[87] Other data-driven approaches have identified important factors relevant to treatment response for a number of widely utilized medications and behavioral approaches.[42,88] By looking deeper into the low treatment rates and investigating factors that impact treatment success, clinical researchers can more readily identify opportunities to improve the landscape of AUD.

Conclusions

AUD is a complex clinical phenomenon, with multiple potential pathways to the disorder. By refining our conceptualization of AUD and identifying key factors contributing to its development and maintenance, researchers can uncover opportunities for translation and advancements in treatment. Other clinical resources, such as published practice guidelines (eg, "Practice Guideline for the Pharmacological Treatment of Patients with Alcohol Use Disorder"; APA, 2021), further assist providers by providing specific statements and recommendations on evidence-based treatments for AUD.

There are multiple potential intervention points in the treatment of AUD, including withdrawal management, targeting symptomatic improvement (eg, craving), behavioral/cognitive modification, and relapse prevention. The most extensively supported interventions for AUD include behavioral interventions (eg, cognitive-behavioral therapy and motivational interviewing) and pharmacotherapies (naltrexone and acamprosate). Notably, studies demonstrate that treatment outcomes can be further improved when pharmacotherapies are used in combination with psychosocial treatments.[60,61] The field has also witnessed growing interest in novel technology-based therapeutic approaches, which have the potential to improve overall accessibility and ease of treatment delivery.

The heterogeneity of AUD and the complexity of treatment, coupled with the additional individual- and systemic-level barriers, likely impacts treatment utilization and treatment efficacy among individuals with AUD. It is well known in the field that a "one size fits all" approach to treatment is unlikely to work given the heterogeneity of AUD. Instead, both health-care providers and patients frequently adopt a multifaceted "more is better" approach, integrating various evidence-based resources concurrently to improve the chances of achieving sustained recovery. Additionally, the demonstrated negative health implications of alcohol consumption, even at light-to-moderate levels, suggest the utility of more population-level interventions and prevention efforts. As the field of AUD treatment continues to prioritize the advancement of novel therapeutic options, this current review aims to establish a foundation by summarizing decades of research on diverse treatment options. In highlighting those interventions with the strongest evidence base, we underscore the scientific basis of treatment methodologies and the significance of translating research findings into advancements in patient care.

Disclosure

The authors report no conflicts of interest in this work.

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