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Alcohol Use Disorder Treatment: Problems and Solutions

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alcohol use disorder, AUD, AUD treatment, AUD treatment gap, stigma, screening, brief intervention and referral to treatment, neurobiology of AUD

Abstract

Alcohol use disorder (AUD) afflicts over 29 million individuals and causes more than 140,000 deaths annually in the United States. A heuristic framework for AUD includes a three-stage cycle—binge/intoxication, withdrawal/negative affect, and preoccupation/anticipation—that provides a starting point for exploring the heterogeneity of AUD with regard to treatment. Effective behavioral health treatments and US Food and Drug Administration–approved medications are available but greatly underutilized, creating a major treatment gap. This review outlines challenges that face the alcohol field in closing this treatment gap and offers solutions, including broadening end points for the approval of medications for the treatment of AUD; increasing the uptake of screening, brief intervention, and referral to treatment; addressing stigma; implementing a heuristic definition of recovery; engaging early treatment; and educating health-care professionals and the public about challenges that are associated with alcohol misuse. Additionally, this review focuses on broadening potential targets for the development of medications for AUD by utilizing the three-stage heuristic model of addiction that outlines domains of dysfunction in AUD and the mediating neurobiology of AUD.

SCOPE OF THE PROBLEM

Alcohol misuse constitutes a major source of mortality, social pathology, and burden to the health-care system in the United States. In the United States, data show that over 29 million individuals met the criteria for alcohol use disorder (AUD) in 2019, and more than 140,000 deaths were attributable to alcohol annually from 2015 to 2019 (1, 2). Increases in deaths, hospitalizations, and liver disease that are attributable to alcohol increased dramatically during the first year of the coronavirus disease 2019 (COVID-19) pandemic, and 5% of cancer cases are now attributable to alcohol (3–5).

WHAT IS ALCOHOL USE DISORDER?

Definition

AUD can be defined as a chronically relapsing disorder that is associated with compulsive alcohol drinking, the loss of control over intake, and the emergence of a negative emotional state when alcohol is no longer available (6, 7). Alcohol misuse in AUD can range from a pattern of intermittent episodes of binge alcohol intake to a pattern of prolonged heavy drinking over longer periods of time that progresses to continual drinking for fear of withdrawal.

From a nosology perspective, the diagnosis of AUD is based on positive findings on at least 2 of 11 criteria of the *Diagnostic and Statistical Manual of Mental Disorders*, 5th edition (DSM-5) (8), which provides a framework for the intensity of symptoms with regard to the number of symptoms that an individual presents. The DSM-5 combines earlier diagnostic criteria for alcohol abuse and dependence under the new term AUD, with severity modifiers of mild, moderate, and severe based on the number of criteria that are met. Thus, AUD is now considered a spectrum disorder as described by the DSM-5.

Consistent with the spectrum framework of the DSM-5, an individual can enter the addiction cycle at different stages. Classically, individuals with a substance use disorder, such as AUD, may start with recreational use of the drug during the binge/intoxication stage and progress to the withdrawal/negative affect stage as negative reinforcement evolves (9) (**Figure 1**). However, much of alcohol misuse also develops because negative reinforcement may be the initial starting point via either self-medication (10) or chronic pain (11).

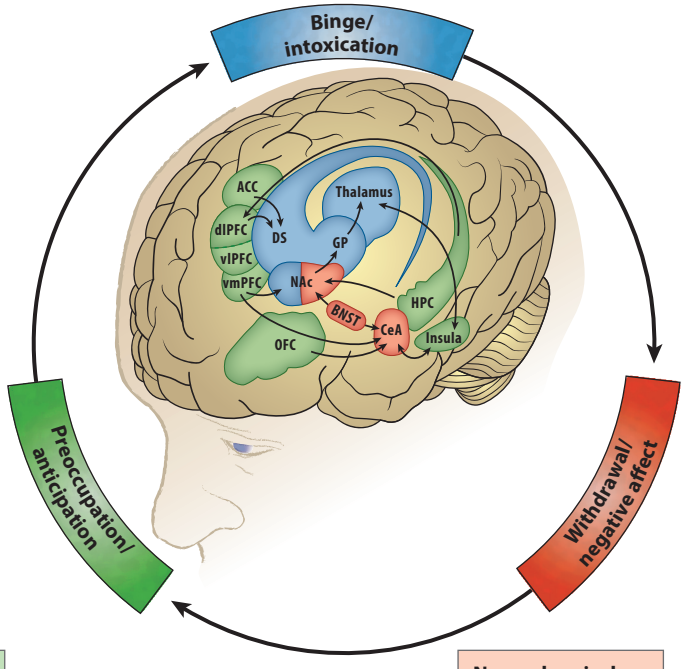
Neurobiological Framework

A heuristic framework for AUD and addiction in general includes a three-stage cycle—binge/intoxication, withdrawal/negative affect, and preoccupation/anticipation—that provides a starting point for exploring the heterogeneity of AUD with regard to treatment (10, 12). Under this addiction framework, stage-related dysregulation occurs in three functional domains (incentive salience/pathological habits, negative emotional states, and executive function) that are mediated by three major neurocircuitry elements (basal ganglia, extended amygdala, and prefrontal cortex, respectively) (10, 13, 14). These three stages feed into each other, become more intense, and ultimately lead to the pathological state of AUD (10) (see the center of **Figure 1**).

From a neurobiological perspective, entrance into the three-stage cycle at any stage can engage neuroadaptations that lead to compulsive-like alcohol consumption. The concept here is that the excessive engagement of reward system activation by alcohol ultimately triggers a break from hedonic homeostasis and subsequent compensatory responses in brain reward and stress systems to generate the negative emotional state of withdrawal (termed hyperkatifeia) (15) of the withdrawal/negative affect stage (10) (**Table 1**). As a consequence—and often in

Neurochemical
- GABA
- Opioid peptides
- Dopamine
- Acetylcholine
- Serotonin
- Norepinephrine
- Glycine/taurine
- Acetaldehyde
- Glutamate
- Allopregnanolone
- BDNF
- Neuroimmune factors

Molecular
- GABA receptors
- Serotonin receptors
- Glycine receptors
- Glutamate receptors: NMDA, kainate, AMPA
- Potassium M channels
- Potassium BK channels
- Calcium channels
- Nucleoside transporter adenosine
- CREB
- Acetylcholine receptors
- G proteins: protein kinases: A, C, γ, ε



Neurochemical
- Dopamine
- Opioid peptides
- GABA
- Glutamate
- CRF
- Glucocorticoids
- Norepinephrine
- Dynorphin/κ-opioid receptors
- Hypocretin
- Substance P
- NPY
- Nociceptin
- Cannabinoids
- Oxytocin

Molecular
- Dopamine D_1, D_2 receptors
- Dopamine transporter
- GluN1, GluN2B receptors
- NMDA and AMPA receptors
- Metabotropic glutamate receptors
- Calpain
- Casein-1ε/δ
- L-type calcium channels
- MTORC1
- ERK1/2
- NF-κB
- Histone methyltransferase

Neurochemical
- Dopamine
- Serotonin
- GABA
- Glutamate
- CRF
- Glucocorticoids
- Norepinephrine
- Hypocretin (orexin)
- Vasopressin
- Substance P
- Neuroimmune factors
- NPY
- Nociceptin
- Endocannabinoids
- Oxytocin

Molecular
- BK channel
- $GABA_A$ receptor subunits
- NPY receptors
- cAMP, CREB
- BDNF
- CRF receptors
- Protein kinases
- Norepinephrine transporter
- microRNA
- Histone dimethyltransferase

(*Caption appears on following page*)

Figure 1 (*Figure appears on preceding page*)

Neurochemical and molecular targets of alcohol in the binge/intoxication, withdrawal/negative affect, and preoccupation/anticipation stages of the addiction cycle. The three stages are hypothesized to be mediated by three key superstructures of motivational circuitry: basal ganglia for the binge/intoxication stage (*blue*), extended amygdala for the withdrawal/negative affect stage (*red*), and prefrontal cortex for the preoccupation/anticipation stage (*green*). These stages and corresponding structures are associated with incentive salience/pathological habits, reward deficits/stress surfeits, and executive function deficits, respectively. Neurochemical targets are listed in the left-hand box for each stage of the addiction cycle. Molecular targets are listed in the right-hand box for each stage of the addiction cycle. Abbreviations: ACC, anterior cingulate cortex; BDNF, brain-derived neurotrophic factor; BNST, basal nucleus of the stria terminalis; CeA, central nucleus of the amygdala; CREB, cyclic adenosine monophosphate response element binding protein; CRF, corticotropin-releasing factor; dlPFC, dorsolateral prefrontal cortex; DS, dorsal striatum; ERK1/2, extracellular signal-regulated kinase 1/2; GABA, γ-aminobutyric acid; GluN, glutamine; GP, globus pallidus; HPC, hippocampus; Insula, insular cortex; MTORC1, mammalian/mechanistic target of rapamycin complex 1; NAc, nucleus accumbens; NF-κB, nuclear factor κB; NMDA, *N*-methyl-D-aspartate; NPY, neuropeptide Y; OFC, orbitofrontal cortex; vlPFC, ventrolateral prefrontal cortex; vmPFC, ventromedial prefrontal cortex. Figure adapted with permission from Reference 7.

parallel—executive function is compromised, thus contributing to deficits that are associated with the preoccupation/anticipation stage and leading to craving for alcohol and perpetuating the addiction cycle (13, 14).

THE GOOD NEWS: EFFECTIVE BEHAVIORAL HEALTH (NONPHARMACOLOGICAL) TREATMENTS FOR ALCOHOL USE DISORDER

Standards in the field of AUD treatment include behavioral health (i.e., nonpharmacological) treatments, such as self-help groups and inpatient and outpatient clinical settings. Evidence-based behavioral health treatments can help patients develop skills to stop or reduce drinking; manage emotions, stress, and cues that trigger drinking; and establish a framework that will support ultimate treatment goals. Evidence-based nonpharmacological treatments, all of which are equally effective, include cognitive-behavioral therapy, motivational enhancement therapy, acceptance- and mindfulness-based interventions, contingency management approaches, couples and family counseling, and 12-step facilitation therapy (16). Although technically not a treatment per se, in-person or online mutual support groups help many people. Such groups have diverse frameworks and can be spiritual based (e.g., Alcoholics Anonymous) and also secular (e.g., Secular Alcoholics Anonymous). Meta-analyses of Alcoholics Anonymous and 12-step facilitation found that they are as effective as other behavioral health treatments at reducing drinking intensity, promoting abstinence, and reducing alcohol-related consequences at 12 months (17). Although brief interventions (see below) can be conducted by primary care physicians and medications for AUD can be prescribed, licensed professional therapists are recommended for evidence-based behavioral health treatments for AUD.

Nonpharmacological treatments can also increase the response to medications by modifying attitudes and behaviors that are related to alcohol, increasing healthy life skills, and helping people stay in treatment. Indeed, most clinical trials that have tested the development of medications for the treatment of AUD have evaluated a medication that is given in addition to either the routine AUD treatment that patients would ordinarily receive in that setting or a manual-guided form of behavioral therapy (e.g., AlcoholFree) (18), motivation enhancement therapy (19), cognitive behavioral coping skills behavioral therapy (20), and 12-step facilitation therapy (21). The National Institute on Alcohol Abuse and Alcoholism (NIAAA) Alcohol Treatment Navigator (**https://alcoholtreatment.niaaa.nih.gov**) is a website that is designed to assist in locating clinicians who provide evidence-based behavioral and/or pharmacological treatments for AUD (**Table 2**).

Table 1 Definitions relevant to the three-stage heuristic framework and neurobiology of alcohol use disorder

Term	Definition
Anhedonia	Anhedonia is generally defined as an inability to experience pleasure in normally pleasurable acts or markedly diminished interest or pleasure in all, or almost all, activities most of the day, nearly every day (8). Less pleasure from situations and stimuli that normally induce pleasure or hedonia is a common element of withdrawal from all drugs of abuse (89) and is considered to be a subset of the hypersensitivity to negative emotional states that is defined as hyperkatifeia.
Basal ganglia	The basal ganglia, or basal nuclei, comprise a group of subcortical nuclei that are situated at the base of the forebrain and top of the midbrain. Basal ganglia are strongly interconnected with the cerebral cortex, thalamus, and brainstem in what are known as cortical-striatal-pallidal-thalamic-cortical loops (90). The basal ganglia are associated with various functions, including the control of voluntary motor movements, procedural learning, habit learning, conditional learning, and emotion.
Executive function	Executive function can be conceptualized as the ability to organize thoughts and activities, prioritize tasks, manage time, and make decisions. To accomplish such complex tasks in the context of the neurobiology of addiction, the prefrontal cortex can be divided into two opposing systems: Go system and Stop system. The Go system engages habit systems, possibly even subconsciously and automatically. The Stop system inhibits such systems. The interactions between these two system produce the well-known impulsivity that is associated with the addiction process during both the initiation of drug intake and relapse (14).
Extended amygdala	The extended amygdala is composed of several basal forebrain structures, including the bed nucleus of the stria terminalis, the central nucleus of the amygdala, and a transition area in the medial portion (shell) of the nucleus accumbens. Major neurotransmitters in the extended amygdala that are hypothesized to play a role in hyperkatifeia, which drives negative reinforcement, include corticotropin-releasing factor, norepinephrine, dynorphin, vasopressin, orexin (hypocretin), substance P, glucocorticoids, and neuroimmune factors. Neurotransmitter systems in the extended amygdala that may buffer negative emotional states include neuropeptide Y, nociceptin (orphanin FQ), endocannabinoids, and oxytocin.
Hyperkatifeia	Hyperkatifeia (derived from the Greek *katifeia* for dejection or negative emotional state) is defined as an increase in intensity of the constellation of negative emotional or motivational signs and symptoms of withdrawal from drugs of abuse. Hyperkatifeia can be considered an emotional parallel to the hyperalgesia (i.e., greater sensitivity to physical pain) that is observed with the repeated administration of chronic opioids and alcohol (15, 91).
Incentive salience	Incentive salience can be defined as motivation for rewards that derive from one's physiological state and previously learned associations about a reward cue that is mediated by the mesocorticolimbic dopamine system.
Pathological habits	Pathological habits are hypothesized to result from the pathological coupling of drug-influenced motivational states and a rigid stimulus response habit system. Drug-seeking and drug-taking habits in individuals with substance use disorder are also reinforced by Pavlovian conditioning, in which drug-associated conditioned stimuli in the environment act as conditioned reinforcers and support protracted sequences of behavior, often in the absence of the outcome.
Prefrontal cortex	The prefrontal cortex plays a key role in mediating executive function, such as planning, response selection, decision making, working memory, personality expression, cognitive flexibility, inhibition, social behavior, and self-knowledge (92).
Reward deficits	Reward deficits refer to the loss of pleasure as reflected in anhedonia or hypohedonia and are measured in humans and animal models by elevations of intracranial self-stimulation reward thresholds (93) and in humans by various self-report scales (85) and some operational tasks that reflect anhedonia such as the monetary incentive delay task (94).
Stress surfeit	Stress surfeit refers to hyperactivation of the hypothalamic-pituitary-adrenal axis and brain stress neurocircuits, resulting in anxiety, irritability, and hyperkatifeia in the context of addiction (91, 95, 96).

Table 2 Online sources for further information

Information	Source	URL
Excess alcohol deaths	Substance Abuse and Mental Health Services Administration	**https://www.samhsa.gov/data/sites/default/files/reports/rpt39441/NSDUHDetailedTabs2021/NSDUHDetailedTabs2021/NSDUHDetTabsSect5pe2021.htm**
	Centers for Disease Control and Prevention	**https://www.cdc.gov/alcohol/features/excessive-alcohol-deaths.html**
Interventions available for the treatment of alcohol use disorder	National Institute on Alcohol Abuse and Alcoholism	**https://alcoholtreatment.niaaa.nih.gov**
Patterns of drinking behavior, effects on health, and prevention	National Institute on Alcohol Abuse and Alcoholism	**https://www.rethinkingdrinking.niaaa.nih.gov**
		https://www.collegedrinkingprevention.gov/collegeaim/
	Centers for Disease Control and Prevention	**https://www.cdc.gov/alcohol/fact-sheets/alcohol-use.htm**
Guidelines of what to eat and drink to meet nutrient needs, promote health, and help prevent chronic disease	US Department of Agriculture	**https://www.dietaryguidelines.gov/resources/2020-2025-dietary-guidelines-online-materials**
Symptoms, causes, risk factors, and diagnosis of alcohol use disorder	WebMD	**https://www.webmd.com/mental-health/addiction/what-is-alcohol-abuse#1**
Drug and device development processes	US Food and Drug Administration	**https://www.fda.gov/patients/learn-about-drug-and-device-approvals**
Overcoming obstacles (valleys of death) in drug development	Foundation for Sarcoidosis Research	**https://www.stopsarcoidosis.org/fsr-dia-2017/**
Good laboratory practice for nonclinical laboratory studies	US Food and Drug Administration	**https://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfcfr/CFRSearch.cfm?CFRPart=58**
Economic costs of substance use disorders in the United States	Recovery Centers of America	**https://recoverycentersofamerica.com/resource/economic-cost-of-substance-abuse-disorder-in-united-states-2019**
	Centers for Disease Control and Prevention	**https://www.cdc.gov/alcohol/features/excessive-drinking.html**
The Healthcare Professional's Core Resource for identifying, managing, and treating alcohol use disorder	National Institute on Alcohol Abuse and Alcoholism	**https://www.niaaa.nih.gov/health-professionals-communities/core-resource-on-alcohol**

MORE GOOD NEWS: THERE ARE EFFECTIVE US FOOD AND DRUG ADMINISTRATION–APPROVED MEDICATIONS FOR THE TREATMENT OF ALCOHOL USE DISORDER

Three medications are currently approved for AUD in the United States and are an effective and important aid for the treatment of people with this condition (**Figure 2**). Indeed, they are as effective for the treatment of AUD as antidepressants are for the treatment of depression (22). Unfortunately, there is a lack of understanding of their efficacy among the general public,

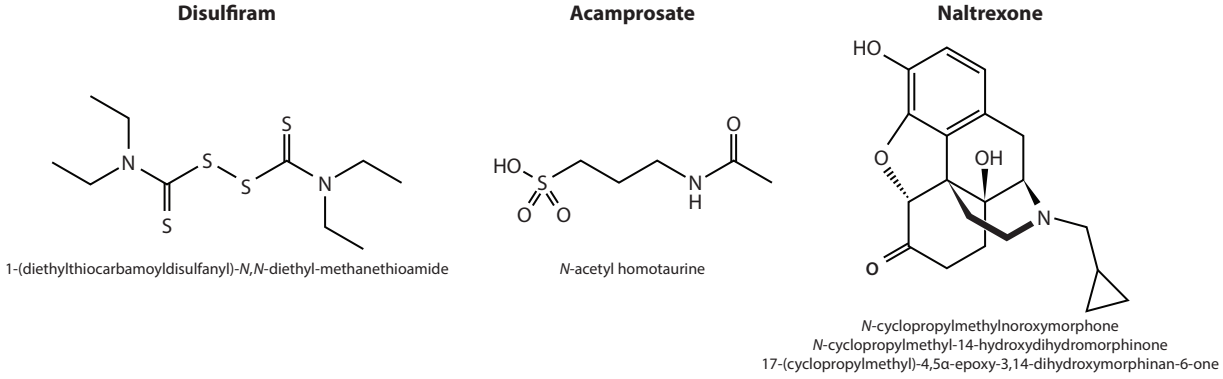


Figure 2

Currently approved medications for alcohol use disorder in the United States. Disulfiram is an acetaldehyde dehydrogenase inhibitor that raises blood acetaldehyde levels if one drinks, resulting in an aversive reaction. This aversive reaction includes flushing, nausea, vomiting, and multiple physiological symptoms. Acamprosate is a taurine derivative (calcium homotaurine) that blocks craving for alcohol during abstinence by restoring homeostasis in hyperglutamatergic neurotransmission during acute and prolonged withdrawal from chronic alcohol drinking that is associated with alcohol use disorder. Naltrexone is an opioid receptor antagonist/inverse agonist that blocks rewarding effects of alcohol presumably by blocking the alcohol-induced activation of endogenous opioid peptides.

basic scientists, and health-care professionals. As outlined below, there is very poor utilization of treatment in general and medications in particular.

Disulfiram

Disulfiram, approved by the US Food and Drug Administration (FDA) as a pharmacotherapy for AUD in 1951, is an aldehyde dehydrogenase inhibitor. If a person is taking disulfiram, then even small amounts of alcohol produce a buildup of acetaldehyde in the blood and a rapid onset of an aversive disulfiram-alcohol reaction. This aversive reaction includes flushing, nausea, vomiting, and multiple cardiac and respiratory symptoms that can be fatal in severe reactions. A person's fear of this strong disulfiram-alcohol interaction may comprise the primary mechanism of disulfiram's deterrent effect, as opposed to the drug's pharmacodynamic properties (23). Medication adherence is a problem with disulfiram (24), and outcomes are optimized with supervised administration (e.g., by a spouse or roommate) in compliant patients (25). A meta-analysis of randomized, open-label trials found a moderate effect of disulfiram relative to various comparison groups; the effect of disulfiram was found to be large under conditions of supervised administration (23). Disulfiram has more serious adverse events than comparison treatments (23), and the alcohol-disulfiram interaction has inherent risks, which in some patients can strengthen their motivation to abstain from alcohol. The potential benefit of disulfiram for appropriately selected patients who prefer this treatment has been found to outweigh the harms, particularly given the risks of continued alcohol use (26). Many have found disulfiram to be well tolerated when taken as prescribed (27).

Naltrexone

Naltrexone is an opioid receptor antagonist/inverse agonist that was approved by the FDA for the treatment of alcohol dependence as an oral preparation in 1995 and as a long-acting injectable in 2006. The rationale for opioid receptor antagonism as a treatment strategy for AUD is based on the premise that naltrexone blocks the rewarding effects of alcohol, a hypothesis that is supported by numerous preclinical and clinical studies (28). A systematic review and meta-analysis

that included 53 randomized controlled trials of oral naltrexone (50 mg) for the treatment of AUD found that the number of people needed to treat was 12 for naltrexone to significantly decrease the likelihood of returning to heavy drinking (29).

Problems with medication nonadherence with oral naltrexone (30) led to the development of a long-acting (30-day) injectable formulation. A meta-analysis found a higher risk of discontinuation due to adverse events with naltrexone compared with placebo. Common side effects included nausea, vomiting, and dizziness (29). Patients who receive Vivitrol (naltrexone for extended-release injectable suspension) may also experience injection site reactions. Naltrexone is metabolized in the liver and is contraindicated in patients with acute hepatitis and liver failure.

Acamprosate

Acamprosate (calcium homotaurine) was developed in France. Its first preclinical study showed that it decreased dependence-induced drinking in rats (31). The FDA approved acamprosate for the maintenance of abstinence in detoxified alcoholics in 2004. A meta-analysis of 27 randomized controlled trials of acamprosate found that the number needed to treat to prevent a return to any drinking was 12 (29).

One prominent action of acamprosate in AUD is to restore homeostasis in hyperglutamatergic neurotransmission during acute and prolonged withdrawal (32). Consistent with this hypothesis, acamprosate reversed the increases in brain glutamate in alcohol-dependent rats (33) and in humans with AUD (34). In a pharmacometabolomic study, serum glutamate was identified as a biomarker of an acamprosate response in alcohol-dependent patients (35). Additionally, baseline serum glutamate levels were significantly higher in responders compared with nonresponders, and serum glutamate levels in responders were normalized after acamprosate treatment, whereas there was no significant change in glutamate in nonresponders (35). Acamprosate is not metabolized by the liver and is instead excreted primarily by the kidney. The use of acamprosate is contraindicated in patients with severe renal impairment (36, 37).

MEDICATIONS REPURPOSED FOR THE TREATMENT OF ALCOHOL USE DISORDER RECOMMENDED BY THE AMERICAN PSYCHIATRIC ASSOCIATION PRACTICE GUIDELINE

Topiramate and gabapentin are drugs that were originally developed as antiepileptic medications and that have therapeutic potential for AUD in patients who (*a*) seek to decrease or quit drinking, (*b*) prefer topiramate or gabapentin, (*c*) are intolerant to or have not responded to acamprosate and naltrexone, and (*d*) have no contraindications to the use of these medications (26).

Topiramate (Topamax and generic) was FDA approved as an oral antiepileptic drug in 1998 and for migraine prophylaxis in 2004. Topiramate is hypothesized to attenuate alcohol's reinforcing effects by facilitating γ-aminobutyric acid (GABA)-ergic function and inhibiting glutamatergic function (38). A meta-analysis of randomized controlled trials found decreases in heavy drinking days with topiramate (29). However, patients with AUD who were treated with topiramate had a higher risk of cognitive dysfunction, paresthesias, and taste abnormalities compared with placebo-treated patients (29).

Gabapentin (Neurontin and generic) was approved by the FDA as an oral antiepileptic drug in 1993 and as a treatment for postherpetic neuralgia in 2002. It is a selective inhibitor of calcium channels (39), which results in multiple antiexcitatory, proinhibitory neurotransmitter actions (40). Gabapentin has shown efficacy for the treatment of AUD in both human laboratory studies and clinical trials (41–43). An often-reported secondary benefit of gabapentin for the treatment of AUD is a beneficial effect on sleep (43).

CURRENT CHALLENGES FOR THE TREATMENT OF ALCOHOL USE DISORDER

Treatment Gap

The treatment gap refers to the dramatic disconnect between individuals in the United States who need treatment for AUD and those who receive treatment. Estimates suggest that less than 8% of adult individuals who need treatment receive any treatment (behavioral or medical) within 1 year (44). In 2019, less than 2% received one of the FDA-approved medications (45). The reasons for this treatment gap are numerous and include a lack of knowledge, a lack of screening and brief intervention, a lack of referral to treatment, a lack of available treatment facilities, and stigma.

The lack of knowledge involves general misconceptions that AUD can only be treated in 28-day inpatient rehabilitation programs and programs that advocate complete abstinence, such as Alcoholics Anonymous, when, in fact, AUD is a spectrum disorder that involves levels of engagement in the disorder, ranging from mild to moderate to severe. It follows that treatments should parallel severity and involve a wide spectrum of interventions (NIAAA Alcohol Treatment Navigator; **https://alcoholtreatment.niaaa.nih.gov**; **Table 2**).

Other knowledge gaps include a general lack of understanding of what constitutes a standard drink, of what constitutes dietary guidelines for moderate drinking, and that the FDA-approved medications are effective. Defining a standard drink should be a first step in educating the public about unhealthy drinking. For example, a standard drink in the United States is considered 12 oz of beer, 5 oz of wine, and 1.5 oz of distilled beverage (46; **https://www.rethinkingdrinking.niaaa.nih.gov**). The dietary guidelines for moderate drinking that are outlined by the US Department of Agriculture are 2 drinks per day or 14 drinks per week for males and 1 drink per day or 7 drinks per week for females (47). Evidence also suggests that few people (public and healthcare professionals) know of the three FDA-approved medications for the treatment of AUD (48) (**Table 2**).

Lack of Uptake of Screening, Brief Intervention, and Referral to Treatment

Another common reason why individuals with AUD do not seek treatment is that they do not consider themselves to have a drinking problem or may never have been told they have AUD (49). The fact that individuals do not consider themselves to have a drinking problem highlights the importance of adequate screening and accurate diagnosis as a first step in treating AUD. The screening, brief intervention, and referral to treatment (SBIRT) (50) model is an evidence-based approach to early detection and intervention for those at risk of developing AUD. The US Preventive Services Task Force (USPSTF) recommends alcohol SBIRT or counseling in primary care settings for adults 18 years of age and older (51).

For example, Mintz et al. (52) used 2015–2019 National Survey on Drug Use and Health data to examine very basic screening, advice, and referral for people with AUD. In their sample of 214,505 people, there was a weighted prevalence of AUD of 7.8%. Examining cascades of care, 81.4% of people with AUD saw a clinician in the past year, and 69.9% were asked at least one question about their alcohol consumption, most likely on an intake form (screening). However, among people who were screened, only 11.6% were offered advice/information (brief intervention), and only 5.1% were advised about treatment options or other resources (referral to treatment) (52). People with severe AUD were more likely to receive advice (23%) and/or referral (12.5%), but these levels are quite low. Importantly, screening for alcohol misuse can also help clinicians spot other health-related issues, and primary care settings represent a key place and opportunity for the implementation of AUD treatment.

The SBIRT model requires little effort by a health-care clinician. Although simple quantity-frequency questions do not provide a diagnosis of AUD, a single standardized screening question was found to effectively detect unhealthy alcohol use: "How many times in the past year have you had *X* or more drinks in a day?" where *X* is 5 for men and 4 for women, and a response of 1 or greater is considered positive (53). The SBIRT model also includes a brief intervention using motivational interviewing. Brief interventions were effective in reducing alcohol consumption compared with controls at 1-year follow-up with comparable efficacy in men and women (54). If clinical follow-up shows that the brief intervention was ineffective in reducing alcohol use, then evidence-based pharmacological and behavioral treatments for AUD should be provided (referral to treatment).

Finally, the treatment gap is perpetuated by the lack of treatment facilities in the United States for addiction and psychiatric disorders in general (55). An inadequate capacity for the treatment of substance use disorders in general continues to be an issue, and evidence suggests that long waiting lists remain a major impediment to treatment (56, 57). In general, outpatient treatment is inadequate, and more inpatient hospital beds are needed (58).

Challenges for Medication Development

One major challenge is the long process between identifying possible treatment targets for AUD and the approval of a medication by the FDA. For example, the search for naltrexone began in 1980 with a preclinical study in an animal model (59). Naltrexone was approved by the FDA 15 years later (in 1995). The search for acamprosate began in 1987 with a preclinical study in an animal model (31) and was approved by the FDA 17 years later (in 2004).

Research on the neurobiology of AUD has identified numerous potential targets for the treatment of AUD within the framework of the three-stage cycle of addiction and three major domains of dysfunction (see **Figure 1**). However, there remain many challenges for medication development. These include valleys of death on the way to FDA approval and ultimate marketing of the drug, stigma, and pharmaceutical industry commitment (60; **https://www.fda.gov/patients/learn-about-drug-and-device-approvals**) (**Table 2**). Valleys of death are the obstacles that block innovative medical research discoveries (in this case, medications) from becoming new therapies or even the initiation of clinical trials (**https://www.stopsarcoidosis.org/fsr-dia-2017/**), and these valleys of death follow the FDA approval process.

The first step in the FDA approval process for a drug involves research and development, comprising investigational processes in the identification of new drugs that interface with neurofunctional domains of the three cycles of AUD. Information is then gathered on pharmacokinetics, effectiveness in animal models, and initial studies of toxicity.

The second step in the FDA approval process requires studies of potential toxicity. Before testing a drug in people, the potential of the drug to cause toxicity is studied using both in vitro and in vivo testing of serious harm, also called toxicity, using good laboratory practices (61).

The third step in the FDA approval process involves clinical research with humans. Here, the sponsor must submit an investigational new drug (IND) application to the FDA before beginning clinical research. The IND application includes animal efficacy and toxicity data, manufacturing information, clinical protocols for studies to be conducted, data from any prior human research, and information about the investigator (**Table 2**). There are then four phases of clinical trials. Phase I is primarily for safety and dosage determination. Approximately 70% of drugs move to the next phase. Phase II trials test efficacy and side effects. Approximately 33% of drugs move to the next phase. Phase III trials are designed to test efficacy and monitor adverse reactions, and only 3–25% move to the next phase. The fourth step involves FDA approval. At this point, the drug developer has established from preclinical and clinical research that the drug is safe and effective

for its intended use, which is all outlined in the new drug application (NDA). The NDA must include everything that is known about the drug from preclinical to Phase III clinical trials. The NDA is then reviewed by an FDA advisory committee, a process that can take up to 6–10 months.

Pharmaceutical Industry Commitment

A 34% increase in the number of drug development programs comprising the clinical pipeline for addiction pharmacotherapies occurred over the past 5 years (29 programs in 2018 versus 39 programs in 2022; 8 programs in 2019 versus 9 programs in 2023), but this is very low compared with other major diseases and disorders (62). A 2021 report showed that despite a surge in biotechnology industry funding, the amount of venture capital funding for novel addiction drug programs was $130 million over the past 10 years, 270 times less than for oncology (62). The estimated economic cost in the United States for substance use disorders was $500 billion in 2019 according to the Recovery Centers of America (63) and $249 billion for AUD specifically (64). These costs include indirect costs that are attributable to job losses, early deaths, and other social impacts (e.g., criminal activity), in addition to direct health-care costs (**Table 2**).

Several factors appear to contribute to this lack of funding by industry, including the lack of novel chemical entities in the clinical pipeline as exemplified by only one new chemical entity being FDA approved in the past 5 years (i.e., lofexidine for opioid use disorder) (62, 65). Novel addiction treatments also have one of the lowest Phase II success rates (14 of 15 programs failed in the last decade) (62). Thus, for addiction and particularly AUD, venture capital funding is very low, the number of companies that engage in developing addiction therapies is very small, most of the targets are not novel identities (as defined by no FDA approval history: only 9 of 39), and the approval rate for medications is very low (62).

Why is there so little interest in, and pursuit of, medications for addiction, particularly for AUD? Some factors are inherent to the process (e.g., cost, success rate of trials, and perceived return on investment). Other issues are that policy decisions have not incentivized innovation, instead favoring reimbursement with existing generic addiction treatments and coverage, and the need to change reimbursement policies to increase investment in new entities (62). One contribution to the lack of a perceived return on investment involves negative perceptions about AUD as a treatable disorder and the stigma that AUD is a moral problem and not a brain disorder (66).

Stigma

Words matter when it comes to the widespread stigma regarding people who struggle with alcohol misuse. Research on stigma for AUD in various countries found that people with AUD were more likely to be deemed as at fault for their condition than people with a range of mental disorders and dementia (67). Stigma is also associated with decisions to pursue care in mental health (68). As noted above, fewer than 1 in 10 people with AUD get help each year, and 20% of people who do not receive care indicate concern that it might cause neighbors or their community to have a negative opinion of them (69). Stigma also impacts the care of those in need of liver transplants due to long-term excessive alcohol consumption (70). Indeed, in the context of clinical trials, personal stigmas about addiction are viewed as constraining clinical trial enrollment because many patients are reluctant to seek help (62).

NOVEL SOLUTIONS FOR THE TREATMENT OF ALCOHOL USE DISORDER: CLOSING THE TREATMENT GAP

Given the diverse biological processes that contribute to AUD, new treatments are needed to provide a broader spectrum of therapeutic options (58). Some people may respond to a behavioral

or medication treatment that helps with craving. Others may respond to a medication that relieves impulsivity. Still others may respond to agents that reverse the negative emotional state of withdrawal or protracted withdrawal. As with other medical conditions, people with substance use disorders should have a range of treatment options. Scientists are working to develop a larger menu of therapeutics that could be tailored to individual needs.

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

Reductions of drinking can be clinically meaningful, and the FDA accepts abstinence and no heavy drinking days as primary outcomes for Phase III trials of AUD pharmacotherapy (71). A heavy drinking day is defined as 4 or more (in women) or 5 or more (in men) drinks in a day. However, studies showed that World Health Organization (WHO) 1- and WHO 2-level reductions of risk levels are associated with clinically meaningful benefits, reductions of alcohol-related consequences, and improvements in mental health (72, 73). WHO risk levels are defined by the amount of alcohol consumed per day (low risk: 1–40 g for males, 1–20 g for females; medium risk: 41–60 g for males, 21–40 g for females; high risk: 61–100 g for males, 41–60 g for females; very high risk: ≥101 g for males, ≥61 g for females) (74).

A secondary analysis of three multisite AUD pharmacotherapy trials to evaluate WHO 1- and 2-level reductions of drinking as AUD treatment outcome measures showed that the WHO drinking risk level reduction was equally or more sensitive to treatment compared with FDA-accepted outcomes, implying that this measure could be an outcome indicator of treatment efficacy in AUD therapeutic trials (75). Additionally, using a secondary data analysis with logistic regression of individuals with AUD in a large, multisite, randomized, placebo-controlled clinical trial, 1- and 2-level reductions of WHO risk levels during alcohol treatment were maintained after treatment and associated with better functioning over time (76). Both studies suggest that the use of WHO risk level reductions as an outcome measure that may reflect clinically significant improvement in how individuals who seek treatment for AUD feel and function may make Phase III clinical trials more attractive for medication development by the pharmaceutical industry.

Engaging Screening, Brief Intervention, and Referral to Treatment

As noted above, research has shown that screening and brief intervention are cost effective in primary care settings, can reduce alcohol use, and prevent the burden of pathology in individuals who are engaged in alcohol misuse (77–79).

For the screening of adults, the USPSTF recommends the Alcohol Use Disorders Identification Test–Consumption (51). The USPSTF also recommends the NIAAA single alcohol screening question, which asks, "How many times in the past year have you had *X* or more drinks in a day?" where *X* is 5 for men or 4 for women. Brief interventions in health-care settings and visits to primary care can include feedback on patients' current level of alcohol use risk and potential health-related harms, the identification of common situations in which they drink at risky levels, clear advice to reduce drinking, and agreement on a plan to reduce drinking (80; see below). For individuals with major alcohol problems or moderate to severe AUD, more intensive therapy that is provided by licensed therapists with a specialty in addiction, including the use of FDA-approved medications for AUD that are provided in primary care or by addiction-specialist physicians, will likely be required (referral to treatment) (81).

Addressing Stigma

The stigma of addiction in general and alcohol in particular requires a change in language usage (62, 82). When clinicians are provided with vignettes that use such terms as "alcohol abuser" rather

than "a person with an alcohol use disorder," they are more likely to view patients in a negative light. The recommendation now is to change the terminology physicians use to "alcohol use disorder" rather than "alcoholism" and to "alcohol-associated liver disease" rather than "alcoholic liver disease" (70, 82). Modifying language reduces stigma, mitigates shame and guilt about problems with alcohol, increases the likelihood a person with an AUD will seek treatment, and facilitates the belief that recovery is possible.

Implementing a Heuristic Definition of Recovery

An operational definition of recovery for AUD was developed based on qualitative feedback from key recovery stakeholders (e.g., researchers, clinicians, and recovery specialists) to facilitate research on recovery (83). Here, recovery is viewed as both a process of behavioral change and an outcome that incorporates time periods for two key components: remission from DSM-5 AUD and cessation from heavy drinking (a nonabstinent recovery outcome). This definition of recovery also emphasizes the importance of biopsychosocial functioning and quality of life in enhancing recovery outcomes. Such a definition will hopefully increase consistency in recovery measurement, stimulate research to better understand recovery, facilitate the process of recovery, and ultimately contribute to closing the treatment gap.

Considering a Conceptual Framework Embracing Earlier Treatment of Addiction

As noted above, treatment penetration rates for AUD are disappointing. One observation is that a significant proportion of the larger population of those who regularly misuse substances is likely to meet the criteria for mild AUD and then often transition to moderate or severe AUD, a progression that has largely been ignored (84). A conceptual framework to provide an operational definition of early-stage AUD has been proposed (84). In this formulation, the DSM-5 diagnostic categories of mild to moderate substance use disorder formed a starting operational definition for preaddiction, which was proposed to engender broader clinical efforts to effect early treatment.

Educating Health Professionals: *The Healthcare Professional's Core Resource on Alcohol*

The Healthcare Professional's Core Resource on Alcohol (80) was developed to provide health-care professionals everything they need to know about alcohol. It consists of 14 concise, user-friendly articles and provides a means of gaining continuing education credit. It is organized into three sections: "Foundational Knowledge," "Alcohol's Clinical Impacts," and "Strategies for Prevention and Treatment." In the "Foundational Knowledge" section, one can find "The Basics," "Risk Factors," "Neuroscience," and "Stigma." In the "Alcohol's Clinical Impacts" section, one can find "Medical Complications," "Alcohol-Medication Interactions," "Mental Health Issues," and "Alcohol Use Disorder." In the "Strategies for Prevention and Treatment" section, one can find "Screen and Access," "Conduct a Brief Intervention," "Recommend Evidence-Based Treatment," "Make Referrals," and "Support Recovery." Finally, there is the additional article "Promote Practice Change."

Educating the Public

A number of resources are now available for the general public to understand what constitutes unhealthy drinking, to understand individual differences in vulnerability to pathology that is associated with drinking, and to help individuals find treatment options for alcohol misuse

and AUD. Rethinking Drinking (**https://www.rethinkingdrinking.niaaa.nih.gov**) is a website and print publication to help individuals assess their drinking habits and find ways to make a change. Similarly, the Centers for Disease Control and Prevention has the website Alcohol Use and Your Health (**https://www.cdc.gov/alcohol/fact-sheets/alcohol-use.htm**). College Aim (**https://www.collegedrinkingprevention.gov/collegeaim/**) provides comprehensive information regarding prevention approaches that are found to be effective in college environments. The NIAAA Alcohol Treatment Navigator (**https://alcoholtreatment.niaaa.nih.gov**) is an online resource to help people understand treatment options and locate nearby treatment, including telehealth options.

Broadening Targets Based on the Heuristic Three-Stage Addiction Model

In AUD, as predicted by the three-stage cycle framework and three domains of dysfunction discussed above (see **Figure 1**), a broad spectrum of drug misuse is manifest that can range from binges of alcohol intake to daily episodes or prolonged days of heavy drinking, constant drinking for fear of withdrawal, episodic recovery, craving, and relapse.

A framework and rationale for the Addictions Neuroclinical Assessment (ANA) were established using knowledge of the neurobiological basis of addiction in humans and model organisms (85). Three domains—executive function, incentive salience, and negative emotionality—that are linked to the three stages of the addiction cycle form the core functional elements of addictive disorders. The ANA framework proposes that measurements of these domains in epidemiological, genetic, clinical, and treatment studies will provide underpinnings for understanding cross-population and temporal variations in addictions in general. The ANA also provides a basis for understanding shared mechanisms in addictive disorders, the impact of changing environmental influences, and gene identification. Ultimately, such a deep assessment was hypothesized to involve a combination of neuroimaging and performance measures and was thought to be a key to reconceptualizing the nosology of addictive disorders on the basis of process and etiology, an advance that can lead to better prevention and treatment (85).

Subsequently, several lines of evidence, including a factor analysis of responses on self-reported measures and neuropsychological tests in humans with AUD, have validated the importance of the three-stage cycle/three-domain dysfunction in AUD. These factor analyses showed that measures of three heuristically defined functional domains (incentive salience, negative emotionality, and executive function; **Table 1**) captured many of the effects of genetics and environment that lead to trait vulnerability that is shared across different addictive disorders. In one study, clinical, behavioral, and self-report measures of addiction, personality, cognition, behavior, and exposure to early-life stress were collected as part of a screening and natural history study of AUD in 454 individuals who represented the spectrum of alcohol use and AUD (86). A three-factor model generally demonstrated a good fit with the assessment measures, and the factors closely aligned with ANA domains of incentive salience, negative emotionality, and executive function. Subsequent studies have confirmed the original factor analysis (87).

One potential benefit of this approach is that measures of these domains in a general framework of an ANA may ultimately transform the assessment and nosology of addictive disorders and may be informative for staging disease progression. Another potential benefit is that a focus on the three domains may serve as a bridge to a reformulation of addiction nosology to better capture individual differences among patients for whom the withdrawal/negative affect stage drives compulsive drug taking (88). An analysis using self-report measures from the Matching Alcoholism Treatments to Client Heterogeneity (Project MATCH) and Combined Pharmacotherapies and Behavioral Interventions (COMBINE) studies also showed the utility of domains that are relevant to the addiction cycle in predicting AUD treatment outcomes and recovery. Among individuals

who sought treatment for AUD, negative emotional states and incentive salience were significantly associated with outcomes 1 and 3 years posttreatment, and executive functioning predicted nonabstinent recovery at year 3 (87).

Given the clinical validation of the three domains of dysfunction that are associated with AUD, data from animal models that are relevant to the three stages of the addiction cycle can also be used to identify novel targets for drug development (see **Figure 1**). Compiled from an extensive review of the neurobiology of alcohol addiction (7), this large number of targets emphasizes the gap between basic research and translation to the clinical domain and provides promise for future studies if some of the obstacles that are associated with industry can be overcome.

Binge/Intoxication Stage Targets

In the binge/intoxication stage, the neurobiological mechanism of action of the acute reinforcing effects of alcohol involves the activation of some of the same reward neurocircuitry and neurotransmitters that are implicated in the actions of psychostimulants and opioids, including dopamine and opioid peptides, with a focus on the nucleus accumbens and central nucleus of the amygdala (7, 9, 14). Other neurotransmitters/neuromodulators that interact with these key elements of basal forebrain neurocircuitry to drive incentive salience and pathological habits include GABA, glutamate, acetylcholine, serotonin, norepinephrine, glycine/taurine, acetaldehyde, neurosteroids, growth factors, and neuroimmune factors (see **Figure 1**; **Table 1**).

In addition to the neurochemical systems that play a functional role in mediating the acute rewarding effects of alcohol, the molecular entities as illustrated in **Figure 1** provide potential targets to block the initial actions of alcohol. For example, although alcohol does not bind to any particular receptor, it is hypothesized to act at ethanol-receptive elements, particularly in water-filled pockets of ion receptor proteins. Thus, low-dose alcohol (<10 mM) interacts allosterically with the following molecular entities: *N*-methyl-D-aspartate receptor 2B (NR2B)-containing *N*-methyl-D-aspartate receptors, α1-glycine receptors, α7 nicotinic acetylcholine receptors, δ-containing $GABA_A$ receptors, BK channels, and T-type calcium channels. These initial actions are then translated via various transduction systems, such as protein kinases, or by the activation of gene transcription via the adenosine-induced activation of cyclic adenosine monophosphate (cAMP)-protein kinase A and, ultimately, cAMP response element binding protein (CREB) systems, making them all potential targets for blocking the acute rewarding effects of alcohol (7). Note that molecular genetic studies, including knockout studies, have confirmed some of the more powerful neuropharmacological effects of alcohol, such as on the μ-opioid receptor and neuropeptide Y (NPY) systems (7).

Withdrawal/Negative Affect Stage Targets

In the withdrawal/negative affect stage, withdrawal from chronic alcohol, similar to other addictive drugs, disrupts reward neurotransmitter function (dopamine, opioid peptides, glutamate, and GABA), recruits the brain stress systems [corticotropin-releasing factor (CRF), glucocorticoids, dynorphin, norepinephrine, hypocretin, vasopressin, substance P, and neuroimmune function], and dysregulates the brain antistress systems (NPY, nociceptin, oxytocin, and endocannabinoids), all of which contribute to negative emotional states of withdrawal, termed hyperkatifeia, and excessive drinking during dependence, mediated by negative reinforcement (7, 9, 14) (see **Figure 1**).

In addition to the neurochemical systems that play a functional role in mediating the tolerance and hyperkatifeia that are associated with chronic alcohol use and alcohol withdrawal, the molecular entities as illustrated in **Figure 1** provide potential targets to reset neuroadaptive

actions that are altered by alcohol and return these neuroadaptations to homeostasis. For example, a role for BK channels in tolerance to alcohol can be seen in the worm *Caenorhabditis elegans*, the fruit fly *Drosophila*, and mice, suggesting an evolutionarily conserved mechanism. Other low-dose molecular targets that play a role in tolerance include $GABA_A$ receptors and NPY, both of which are involved in acute withdrawal, thus reflecting the mechanistic interaction between acute withdrawal and tolerance. Molecular mechanisms that are involved in acute withdrawal and protracted withdrawal include neuroadaptations in GABA receptors, cAMP/CREB systems, brain-derived neurotrophic factor, CRF receptors, protein kinases, and histone acetylation, all of which can contribute to molecular loading on within- and between-system neurocircuitry adaptations and may be targets for medication development (7).

Preoccupation/Anticipation Stage Targets

In the preoccupation/anticipation stage, protracted abstinence studies have shown changes in neurotransmitter systems that reflect extensions of changes that are observed in the withdrawal/negative affect stage. Increases in dopamine, opioid peptide, and glutamate function are associated with animal models of craving, such as cue- and context-induced reinstatement (7, 9, 14). Increases in CRF, glucocorticoid, norepinephrine, dynorphin/κ-opioid receptor, hypocretin, substance P, and neuroimmune function and decreases in NPY, nociceptin, endocannabinoid, and oxytocin function in the antistress domain are associated with protracted stress-like effects (7) (see **Figure 1**).

In addition to the neurochemical systems that play a functional role in mediating craving that is associated with the preoccupation/anticipation stage of the addiction cycle, molecular entities as illustrated in **Figure 1** provide potential targets to block animal model surrogates for craving (7). For example, cue- and context-induced reinstatement reflect dopamine transporter overexpression in the nucleus accumbens and extracellular signal–regulated kinase 1/2 overexpression in the basolateral amygdala, and GluR-C α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA) receptor subunit–knockout mice exhibit a blunted cue-induced reinstatement response. Stress-induced reinstatement is associated with the activation of neuroimmune molecular targets, with a prominent role for nuclear factor κB and other proinflammatory factors in the frontal cortex and hippocampus. Mammalian/mechanistic target of rapamycin complex 1 plays a key role in the dendritic translation of synaptic proteins that are associated with alcohol-related memories.

SUMMARY

In summary, AUD imposes a significant burden on society that inflicts significant medical and social costs. In the United States, most afflicted individuals do not receive treatment, and closing this treatment gap is an ongoing challenge. Effective behavioral health treatments and FDA-approved medications are available but greatly underutilized, contributing to a major treatment gap. Given the diverse biological processes that contribute to AUD, new medications are needed to provide a broader spectrum of treatment options. A starting point for exploring the heterogeneity of AUD with regard to treatment includes engaging a heuristic framework for AUD that includes a three-stage cycle—binge/intoxication, withdrawal/negative affect, and preoccupation/anticipation—with three domains of dysfunction that parallel each stage and have been validated and replicated. This review outlined challenges that face the alcohol field in closing the treatment gap, and it offered solutions, including broadening end points for the approval of medications for the treatment of AUD; increasing the uptake of screening, brief intervention, and referral to treatment; addressing stigma; implementing a heuristic definition of recovery; engaging the concept of early treatment; and educating health-care professionals and the public about

challenges that are associated with alcohol misuse. Additionally, broadening potential targets for the development of medications for AUD, based on the three-stage heuristic model, will provide a neuroscience- and neurocircuit-based rationale for reestablishing homoeostatic function in reward, stress, and executive function domains, now known to be the root cause that perpetuates AUD. Such a neuroscientific approach will require a scaling up of the current reductionistic molecular-microcircuit targets under intense investigation in addiction research today but, ultimately, will allow individualized medicinal treatments for AUD that account for diversity in all domains, from gender to culture to individual makeup.

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