Overview of Alcohol Use Disorder

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Alcohol is regularly consumed throughout most of the world, including by nearly half the U.S. population age 12 or older. Heavy drinking, which is also common, contributes to multiple adverse medical, psychiatric, and social outcomes and more than 140,000 deaths annually in the United States. It is the major risk factor for alcohol use disorder (AUD), whose current U.S. prevalence is 11%. However, AUD is undertreated, with less than 15% of individuals with a lifetime diagnosis receiving any treatment. Risk of AUD is nearly equally genetic and environmental. AUD is responsive to psychosocial treatments, including cognitive-behavioral therapy and motivational enhancement therapy. Alcohol affects multiple neurotransmitter systems, and thus pharmacotherapy for AUD is also effective. The three medications approved in the United States to treat AUD—disulfiram, naltrexone (oral and long-acting injectable formulations), and acamprosate—are underprescribed, despite being considered first-line treatments in clinical practice guidelines. Two medications not approved for treating AUD, topiramate and gabapentin, have shown efficacy in treating the disorder and are used off-label. Recent studies of novel drug candidates, including psychedelics and phosphodiesterase-4 inhibitors, are promising additions for the treatment of AUD, although they require further evaluation before being used clinically. Despite the growing availability of efficacious psychosocial and pharmacological treatments for AUD, it remains a highly stigmatized condition. Research aimed at enhancing the identification and treatment of AUD, including precision therapeutics, could broaden the acceptability of AUD treatment, benefiting affected individuals and their families and reducing the stigma associated with the disorder.

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Alcohol is consumed regularly throughout the world. The archeological record points to alcohol entering the human diet in significant amounts roughly 9,000 years ago, as humans began to store surplus food and to develop the ability to direct fermentation (1). It was then that the modest volumes of alcohol produced by wild fermentation were supplanted by beverages with high alcohol concentrations (2).

In the United States, excessive alcohol consumption was established during colonial times, when most Americans believed that alcohol was medicinal and that excessive drinking was due simply to a lack of will (3, 4). In 1790, the average annual consumption rate was 5.8 gallons of absolute alcohol, which increased to 7.1 gallons by 1830 (by contrast, average annual U.S. consumption is currently about 2.3 gallons). Benjamin Rush, a Philadelphia physician and signer of the Declaration of Independence, first published his landmark *Inquiry Into the Effects of Ardent Spirits Upon the Human Body and Mind* in 1785. In this treatise, Rush, whose interest in mental illness included a particular interest in alcohol misuse, described it as a disease rather than a failure of will: "The use of strong drink is at first the effect of free agency. From habit it takes place from necessity" (5, p. 4). Despite broad recognition among informed individuals that Rush had it right, nearly 250 years later the moralistic view of alcohol use disorder (AUD) persists in the public mind and stigmatizes sufferers of the disorder, which can discourage their seeking treatment, particularly early in its developmental course.

CURRENT U.S. RATES OF ALCOHOL CONSUMPTION, BINGE DRINKING, HEAVY DRINKING, AND AUD

The National Survey on Drug Use and Health (NSDUH) provides an annual estimate of alcohol consumption and the prevalence of AUD in the U.S. population. The 2021 NSDUH found that an estimated 133.1 million people (47.5% of those age 12 or older) drank alcohol in the preceding month and that 60 million were binge drinkers (i.e., ≥5 standard drinks for males and ≥4 standard drinks for females on an occasion [6]). The age group most likely to report past-month binge drinking were those in the 18- to 25-year range (9.8 million people, or 29.2%), and those least likely were adolescents 12–17 years of age (995,000 people, or 3.8%). Some 16.3 million people (12.2% of current drinkers) engaged in heavy drinking (binge drinking on 5 or more days in the past month), with an age distribution similar to that for binge drinking.

In NSDUH, AUD diagnoses were made using DSM-5 criteria (7), which reflect a problematic pattern of alcohol use accompanied by clinically significant impairment or distress. Among people age 12 or older in 2021, 29.5 million

people (10.6%) had a current (i.e., past-year) AUD diagnosis, with an age distribution similar to that for past-month binge drinking and heavy drinking.

ADVERSE CONSEQUENCES OF AUD

AUD is commonly accompanied by a variety of psychiatric disorders (e.g., drug use disorders, major depression, bipolar I disorder, and antisocial personality disorder), medical problems (e.g., alcohol withdrawal, liver disease, pancreatitis, and cancer of the head, neck, liver, colon, or rectum), and psychosocial problems (e.g., accidental injuries, aggression, violence, and suicide) (8–11). In addition to this comorbidity, alcohol consumption imposes substantial mortality and economic costs on the United States. Between 2015 and 2019, an average of 140,557 people (97,182 men and 43,375 women) died from alcohol-related causes annually (12), making alcohol the fourth leading preventable cause of death (13). In 2010, the most recent year for which U.S. data were compiled, estimated alcohol-related costs were $249 billion, 77% of which was attributable to binge drinking (14).

NEUROBIOLOGY OF AUD

Alcohol affects multiple neurotransmitter systems. The expectation and consumption of alcohol stimulates dopamine release in the mesolimbic system, where it mediates the pleasurable and stimulating effects of alcohol. Dopaminergic projections to the orbitofrontal and prefrontal cortices regulate motivation and cognitive control (15). Alcohol also interacts with GABAergic, opioidergic, glutamatergic, cannabinoidergic, noradrenergic, and serotonergic neurotransmitter systems (16) and neuroendocrine systems, including the hypothalamic-pituitary-adrenal axis (17).

Initially, the ingestion of alcohol causes changes in neural circuits, which the individual experiences as pleasurable or anxiety reducing. As blood (and brain) alcohol levels decline, these effects are replaced, at least in part, by withdrawal symptoms. With repeated cycles of alcohol use and withdrawal that are characteristic of chronic alcohol use, physiological adaptations occur in the affected circuits. The associated dysregulation of the circuits is accompanied by responses to alcohol-related cues and withdrawal states that promote alcohol seeking and alcohol use, which reflect impaired control (that is, they persist despite adverse consequences) (18). Although the alcohol-related neural circuits interact in complex ways, the neurochemical disruptions that underlie them are amenable to pharmacological interventions for reducing heavy alcohol use in individuals with AUD.

ETIOLOGY OF AUD

AUD has an estimated twin heritability of 49%, with the remainder of the variance in risk attributable to shared and unique environmental factors (19). Over the past 5 years, genome-wide association studies (GWASs) have identified more than 100 independent loci contributing to risk of AUD or problematic alcohol use (20–23). Problematic alcohol use comprises AUD, alcohol dependence, or an elevated problem score on the Alcohol Use Disorders Identification Test (AUDIT), a 10-item self-report screening questionnaire for hazardous and harmful drinking (24). GWASs have differentiated between alcohol consumption measured using the AUDIT-Consumption scale (AUDIT-C; the first three AUDIT questions) and the AUDIT-Problems scale (AUDIT-P; AUDIT questions 4–10). Separate GWASs of the AUDIT-C and AUDIT-P in samples from the UK Biobank and 23andMe (25) identified novel variants contributing to these traits. They also showed significantly different patterns of genetic correlation of the AUDIT-C and AUDIT-P with multiple traits, including psychiatric disorders. GWASs of AUDIT-C scores and AUD (20) from the Million Veteran Program (26) have also shown that these traits have different patterns of genetic correlation with anthropometric and psychiatric traits (Figure 1). A mediation analysis of GWAS findings in this issue of the *Journal* (22) provides additional evidence that although alcohol consumption is highly genetically correlated with an AUD diagnosis, it is not a sufficient cause of the disorder. While showing that the effects of many genetic variants on AUD risk are mediated by alcohol consumption, the study identified variants that *directly* affect AUD risk. These findings can potentially be used to identify individual targets and pathways whose pharmacological manipulation could prevent the transition from heavy drinking to AUD.

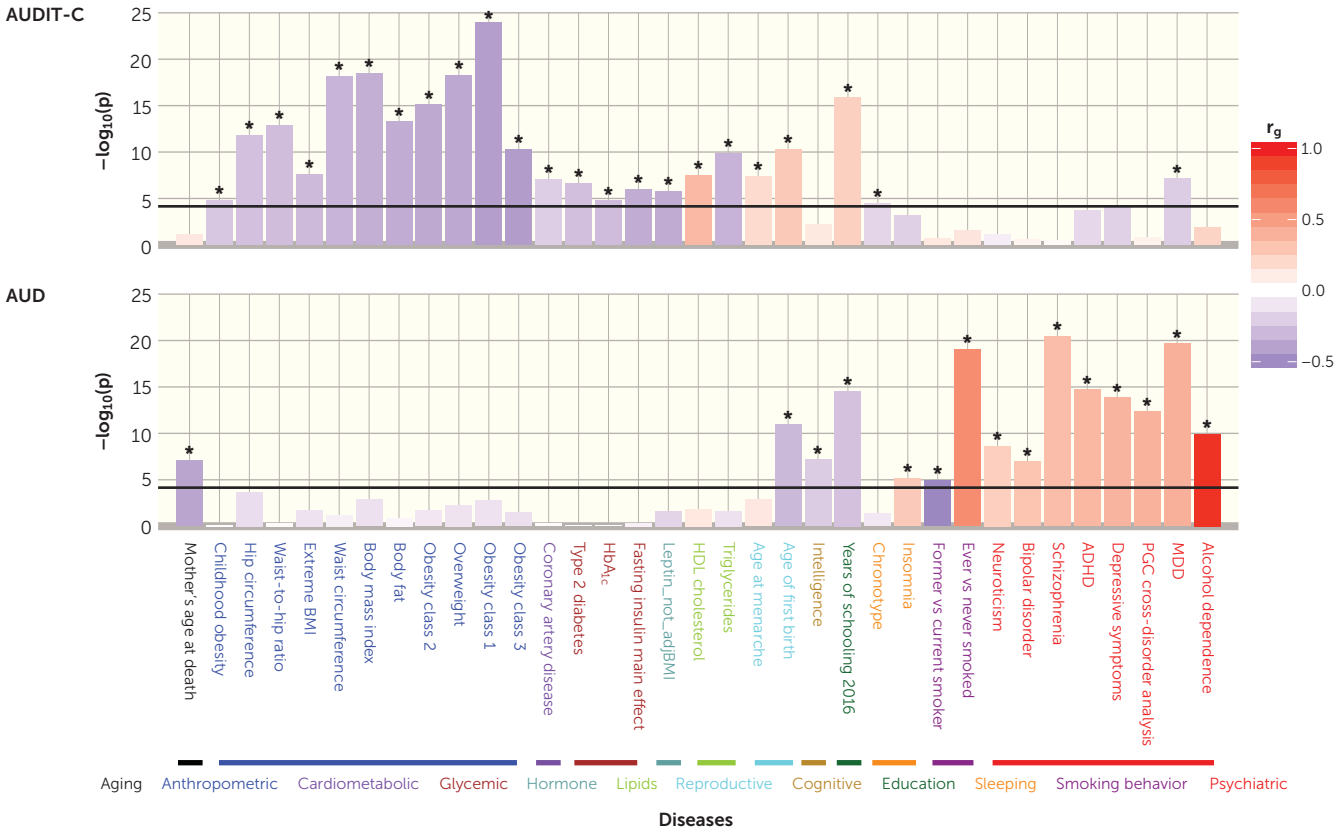
Environmental factors associated with AUD include childhood and adolescent stressors, including verbal, physical, and sexual abuse, and household instability (e.g., physical violence directed at the mother, parental psychiatric and substance use disorders, and incarceration of household members) (27). A strong, graded association between the number of stressors recalled and the risk of AUD and an interaction of stressors with a parental history of AUD are consistent with a model in which environmental factors augment an individual's genetic predisposition to develop AUD (27).

CURRENT TREATMENTS FOR AUD

Psychosocial Treatments

The Department of Veterans Affairs/Department of Defense (VA/DoD) Clinical Practice Guideline (28) recommends the following psychosocial treatments for AUD, the choice of which depends on patient preference and availability: behavioral couples therapy, cognitive-behavioral therapy, community reinforcement, motivational enhancement therapy, and 12-step facilitation. These treatments have demonstrated efficacy in treating AUD (29). For example, in a primarily psychosocial treatment study of 482 alcohol-dependent adults (30), the 30-day abstinence rates 1 year after the initial assessment were 57% in a treatment sample

FIGURE 1. Significant genetic correlations of AUDIT-C score and AUD diagnosis with other traits[a]



[a] Data are from 714 publicly available data sets (221 published and 493 unpublished from UK Biobank) and were tested and corrected for multiple comparisons. Horizontal black lines show the cutoff for Bonferroni-corrected significance, with asterisks showing traits that were significant after correction. The traits are grouped by category and sorted by genetic correlation. ADHD=attention deficit hyperactivity disorder; AUDIT-C=Alcohol Use Disorders Identification Test–Consumption (the first three questions on the AUDIT); MDD=major depressive disorder; PGC=Psychiatric Genomics Consortium. (Figure originally appeared in Kranzler et al., Genome-wide association study of alcohol consumption and use disorder in 274,424 individuals from multiple populations. Nat Commun 2019; 10:1499 [20]).

(N=371) and 12% in a general population group (N=111) (odds ratio=14.67). A larger proportion of individuals in the treated group also reported no binge drinking, psychosocial problems, or alcohol dependence symptoms (40% vs. 23% in the untreated group; odds ratio=7.30).

"Third-wave" modalities, such as acceptance and commitment therapy and mindfulness-based relapse prevention, have also shown efficacy in treating AUD, although they require further investigation before being deployed widely (31). Contingency management, a type of behavioral therapy in which individuals are rewarded for evidence of positive behavioral change, has been evaluated for treating AUD, mostly using monetary-based rewards for tangible evidence of abstinence from alcohol. This approach has also been used to increase appointment attendance and improve medication adherence (32).

However, despite the high prevalence, mortality rate, and economic costs of AUD, in a population survey covering the period 2001–2002, only 14.6% of individuals who met lifetime criteria for AUD reported ever having received any kind of alcohol treatment intervention (33). Most respondents used self-help groups, followed, in descending order, by treatment in an alcohol rehabilitation program, therapy with an individual clinician, hospitalization for detoxification, and enrollment in an outpatient clinic. Two decades later, in 2021, another population survey showed that only 8.3% of 20.7 million people age 12 or older who needed treatment for an alcohol problem received specialty alcohol treatment (6).

Brief counseling, which is suitable for use in primary care settings, can reduce drinking (34), including when administered via the Internet (35). More intensive psychosocial therapies require a trained therapist for their administration. Both types of psychosocial intervention can be combined with pharmacotherapy. The COMBINE study (36), a 4-month treatment trial, compared naltrexone, acamprosate, their combination, or placebo in 1,383 patients. All study groups were randomly assigned to receive either only medical management—a low-intensity, medically based intervention that focuses on medication adherence, monitoring of alcohol use, and direct advice to the patient to reduce or stop drinking—or medical management plus a more intensive treatment that combines established behavioral treatments delivered by licensed behavioral health specialists (37). Outcomes from the COMBINE study are described below.

Pharmacological Treatments

Over the past 70 years, three medications have been approved by the U.S. Food and Drug Administration (FDA) for treating AUD. In 1949, disulfiram was approved based on clinical case series, rather than the large randomized placebo-controlled trials (RCTs) that are the current FDA standard for drug registration. In 1994, the FDA approved oral naltrexone based on two small RCTs (38, 39), and in 2006 the extended-release formulation of naltrexone was approved after a single large RCT (40). The approval of acamprosate in 2004 was based on three pivotal RCTs conducted in Europe (41–43), supported by safety data from a U.S. study (44). Two medications not approved for treating AUD, topiramate and gabapentin, are used off-label.

Although all three FDA-approved oral medications are available as generic drugs and are moderately priced, they are underutilized in treating AUD (45, 46). Nationally, in 2019, only 1.6% of patients with AUD reported receipt of an FDA-approved medication (47). Systematic efforts in the Veterans Health Administration to increase the use of medication-assisted treatment for AUD yielded a prescription rate of only 3.4% (48).

Current recommendations for treating AUD by both governmental agencies (28, 49) and professional societies (50) include medications as first-line treatments. The VA/DoD practice guideline (28) recommends the use of topiramate, disulfiram, acamprosate, and naltrexone as first-line treatments. Similarly, the APA practice guideline recommends that disulfiram, naltrexone, and acamprosate be offered to patients with moderate to severe AUD and that gabapentin or topiramate be offered as alternative treatments (50).

Below, three groups of medications are discussed. In the first group are medications that are FDA approved for treating AUD (disulfiram, naltrexone, and acamprosate). The second group comprises medications that, despite not being FDA approved, have shown substantial evidence of efficacy and are used off-label to treat AUD (topiramate and gabapentin). Medications in the third group are promising novel treatments that require additional supportive evidence before being recommended for clinical use in treating AUD (psychedelics and phosphodiesterase-4 [PDE4] inhibitors). Other medications that have been studied for treating AUD are described in a recent comprehensive review article (51).

FDA-Approved Medications

Disulfiram. Disulfiram inhibits the enzyme aldehyde dehydrogenase, blocking the catabolism of the toxic intermediate metabolite acetaldehyde. Elevation of the plasma acetaldehyde concentration causes a constellation of aversive signs and symptoms that commonly include warmness and flushing of the skin, increased heart rate, palpitations, decreased blood pressure, nausea, vomiting, shortness of breath, sweating, dizziness, and blurred vision. Although severe adverse effects of disulfiram have been reported, they are uncommon. The threat of experiencing the disulfiram-ethanol reaction is thought to discourage drinking.

The dosage of disulfiram approved in the United States is 250 mg/day, although some patients require a higher dosage to evoke a disulfiram-ethanol reaction. Because disulfiram binds irreversibly to aldehyde dehydrogenase, it can take 2 weeks or longer for the patient to no longer be susceptible to a disulfiram-ethanol reaction.

In a 1-year multicenter trial (52), 605 male veterans with AUD were randomly assigned to receive disulfiram (either 1 mg/day or 250 mg/day) or an inactive placebo. Patients in both disulfiram groups were told that they were receiving the drug but were not told the dosage. Although adherent participants in all three groups were more likely to be abstinent throughout the trial, there were no significant differences among the groups in total abstinence, time to first drink, employment, or social stability. In a meta-analysis of 22 studies of disulfiram for treating AUD (seven blinded and 15 open-label studies) (53), which used the primary outcome specific to each trial, the drug was significantly more efficacious than controls only in open-label trials.

Naltrexone. The FDA approval of oral naltrexone for treating AUD was based on its efficacy in preventing heavy drinking in two 12-week single-site RCTs (38, 39). Meta-analyses of subsequent naltrexone trials consistently show the drug to be superior to placebo in reducing the risk of heavy drinking (54–56). The most comprehensive meta-analysis of naltrexone to date (55), which included 53 RCTs and 9,140 participants, found that the number needed to treat to prevent a return to heavy drinking was 12.

An alternative approach to the daily use of oral naltrexone is injectable extended-release naltrexone. Three extended-release naltrexone formulations have been evaluated for treating AUD. The first was a 4-week pilot study of a subcutaneous formulation, which showed a greater reduction in the frequency of heavy drinking than placebo (57). Although a 12-week RCT of an intramuscular formulation (58) did not show a significantly greater reduction in heavy drinking than placebo, it significantly delayed the onset of any drinking following initial abstinence, increased the total number of days of abstinence, and doubled the likelihood of total abstinence. In a 6-month comparison of two active doses of an intramuscular extended-release naltrexone formulation and placebo, only the group receiving the higher dose (380 mg) showed a significantly greater reduction in the rate of heavy drinking than that observed in the placebo group (40). This resulted in its approval by the FDA for treating AUD. In that study, the effect was driven by individuals with >4 days of voluntary abstinence before treatment initiation (~13% of the total sample) (59), and the formulation's package insert calls for abstinence in an outpatient setting prior to initiating treatment.

Combining naltrexone with other medications is another approach to enhancing treatment response. The COMBINE

study, the largest alcohol treatment trial to date (N=1,383) (36), compared naltrexone, acamprosate, both medications, and placebo with either medical management or a more intensive psychosocial treatment, with the medication and psychosocial treatment assignments randomized. The study showed that during treatment, there was a small effect of naltrexone, such that 68.2% of participants who received it had one or more binge drinking days, compared with 71.4% of patients in the placebo group (p=0.02). Naltrexone, when combined with medical management, was associated with abstinence on 80.6% of days, compared with 75.1% in the placebo group (p=0.009). However, the study provided no evidence that combining naltrexone with acamprosate was more efficacious than naltrexone alone on any drinking outcome. Furthermore, although the more intensive psychosocial intervention was more efficacious than medical management alone, it did not enhance medication efficacy (36).

In a 16-week RCT that compared naltrexone only, naltrexone plus gabapentin (for the first 6 weeks only), or double placebo (60), the combined medication group showed a significantly longer time to first heavy drinking day, fewer heavy drinking days, and fewer drinks per drinking day than the other two groups. These differences diminished over the last 10 weeks of the study. Participants with a history of alcohol withdrawal had better outcomes when treated with the naltrexone-gabapentin combination.

Acamprosate. Acamprosate (calcium acetyl-homotaurinate) is a weak NMDA receptor antagonist and an inhibitor of the glutamate metabotropic 5 receptor (61, 62). Three European studies provided the basis for the FDA's approval of the drug for clinical use in the United States. A meta-analysis of 27 acamprosate studies in 7,519 patients (55) estimated a number needed to treat of 12 to prevent a return to any drinking. However, two large multicenter trials in the United States (36, 44), a large European study (63), and an Australian study (64) failed to detect beneficial effects of acamprosate in treating AUD. Additional research is needed to identify which patient characteristics and therapeutic approaches are necessary to ensure a response to acamprosate in treating AUD.

Off-Label Medications

Topiramate. Topiramate is an antiepileptic drug that is also approved for migraine prevention and for weight loss (in a combined formulation with phentermine). In a meta-analysis of seven RCTs (65) (comprising 1,125 participants with AUD), topiramate at a daily dose of 100–300 mg had small to moderate beneficial effects on aggregate measures of abstinence and heavy drinking and concentrations of the liver enzyme γ-glutamyltransferase (GGT). In a recent Bayesian meta-analysis of 13 placebo-controlled RCTs (66) (in 1,397 participants with AUD), topiramate had a moderate effect in increasing the likelihood of abstinence and decreasing the number of heavy drinking days, craving, and GGT concentration.

Topiramate treatment can cause a variety of adverse events, which, although generally mild to moderate in severity, can limit its tolerability. In a meta-analysis (66), paresthesia, drowsiness, and memory impairment were found to be significantly more common with topiramate treatment than with placebo. Uncommon visual adverse events associated with the drug (e.g., blurred vision and myopia), and rare precipitation of glaucoma in individuals susceptible to acute angle closure, require its discontinuation. A slow, gradual increase in the twice-daily dose to the maximum tolerated dosage (e.g., beginning at 50 mg/day and increasing by 50 mg/day weekly over 6–8 weeks) can help minimize topiramate's adverse effects.

Gabapentin. Gabapentin has three FDA-approved indications: as an adjunctive treatment for partial-onset seizures, to manage postherpetic neuralgia, and to treat restless legs syndrome. It is also prescribed off-label for a variety of psychiatric conditions (67). In a meta-analysis of seven RCTs of gabapentin (at dosages ranging from 600 to 3,600 mg/day), estimated effects on six alcohol-related outcomes in a total of 751 individuals with AUD favored gabapentin over placebo, although the only significant difference was on the percentage of heavy drinking days (68).

In a 16-week RCT of gabapentin in treatment-seeking individuals with AUD and recent alcohol withdrawal (69), a significantly greater proportion of evaluable participants in the gabapentin group than in the placebo group had no heavy drinking days (27% vs. 9%; number needed to treat: 5.4). A significantly greater proportion of the gabapentin group (18%) than the placebo group (4%) also reported total abstinence (number needed to treat: 6.2). Whereas these findings were driven by the response in the high-withdrawal-severity subgroup, like the effect seen in the combined naltrexone and gabapentin study described above (60), gabapentin may be most useful for treating AUD in individuals with a history or current high level of withdrawal severity.

Although gabapentin is well tolerated overall, dosages greater than 1,800 mg/day are associated with dizziness, somnolence, ataxia or gait disorder, and peripheral edema (70, 71). Furthermore, an estimated 1% of the U.S. general population misuses gabapentin for recreational purposes, self-medication, or intentional self-harm, either alone or in combination with other substances (including alcohol) (72).

Promising Medications That Require Further Study

Psychedelic drugs. Psychedelic drugs were first studied in the 1970s for treating AUD. In a meta-analysis of six RCTs (73), a total of 536 participants were randomly assigned to receive double-blind treatment with either a single dose of LSD or ephedrine, amphetamine, low-dose LSD, or no medication. LSD-treated participants were nearly half as likely as those in a comparator condition to misuse alcohol at a follow-up 1–12 months after discharge from treatment, an effect that was consistent across studies and yielded a number needed

to treat of 6. LSD was well tolerated in these trials, with no evidence of lasting harmful effects.

Recently, a 12-week RCT of psilocybin was conducted in 93 individuals with AUD, where it was compared with diphenhydramine (74). Medication was administered during two day-long sessions at weeks 4 and 8, with all participants also receiving 12 weeks of manualized motivational and cognitive-behavioral therapy. Both treatments were well tolerated. During the 32-week double-blind follow-up period beginning with the first dose of study medication, the psilocybin group's reported reduction in heavy drinking was double that of the diphenhydramine group (number needed to treat: 4.5). In addition, in the psilocybin group, the likelihood of having no heavy drinking days was triple that of the diphenhydramine group, and the number of alcohol-related adverse consequences was significantly lower than in the diphenhydramine group.

Phosphodiesterase-4 inhibitors. Ibudilast is a well-tolerated anti-inflammatory drug marketed in Japan for treating asthma and poststroke complications. The drug inhibits proinflammatory cytokines and multiple cyclic phosphodiesterases, including PDE4. In a study that combined a laboratory session and a short-term treatment trial (75, 76), ibudilast 100 mg/day was associated with greater reductions in heavy drinking and alcohol cue reactivity than placebo. A 6-week clinical trial aimed at replicating the effects on alcohol consumption is currently under way (NCT05414240). Another PDE4 inhibitor, apremilast, approved by the FDA to treat plaque psoriasis, was studied in an 11-day trial in nontreatment-seeking individuals with AUD at a target dosage of 90 mg/day. Apremilast was associated with a greater reduction in the number of drinks per day and the proportion of heavy drinking days than placebo (77).

Precision Treatments

Precision treatments use a person's genetic or phenotypic characteristics to optimize a therapeutic response. They have been most successful in oncology and cardiovascular medicine but their beneficial effects have not been replicated consistently enough to warrant their use in treating AUD (78, 79). As the literature on the genetics of AUD continues to grow, it will inform the identification of genetic moderators of AUD treatment response. However, the future use of both genetic and phenotypic predictors in treating AUD will depend on whether resources are available to conduct large-scale RCTs that provide adequate statistical power to validate them.

CONCLUSIONS

Considerable progress has been made in understanding the etiology of AUD and enhancing its identification and treatment. Further research can be expected to augment the available treatments and enhance their efficacy. However, because the treatments that are available are not widely used, research is needed on how best to encourage health care providers to incorporate screening and interventions for heavy drinking and AUD in the various settings in which patients with AUD present for care.

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