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Biology, clinical pharmacology and treatment of alcoholism

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Abstract: *Alcohol use disorder (AUD) is a chronic, multifactorial condition shaped by genetic, biological, psychological, and environmental influences. Differences in alcohol sensitivity and vulnerability across populations are partly explained by ethanol metabolism, which is determined by genes encoding alcohol dehydrogenase and aldehyde dehydrogenase. Repeated alcohol exposure progressively remodels neural circuits involved in reward, stress, and executive control, thereby promoting dependence and relapse. Effective management usually requires an integrated approach that combines detoxification support, pharmacotherapy, and behavioral interventions. Approved medications, including disulfiram, acamprosate, and naltrexone, together with structured cognitive therapy and motivational counseling, have demonstrated clinical benefit. However, important questions remain, including why AUD varies so widely between patients, why some individuals recover without formal treatment, how inherited risk is expressed, and how therapy can be better personalized. Further research into neurobiology, pharmacogenetics, and novel therapeutic targets is essential to improve prevention and support sustained recovery.*

Key Word: *Alcohol use disorder, alcoholism, ethanol metabolism, alcohol dehydrogenase, aldehyde dehydrogenase, genetic polymorphisms, neurobiology, pharmacotherapy, behavioral therapy, withdrawal management.*

I.INTRODUCTION

People living with AUD find it hard to rein in their drinking even once it has begun causing clear harm physically, psychologically, or socially and the condition tends to follow a relapsing course. Population research points to sizeable gaps in drinking patterns and alcohol-related harm when comparing racial and ethnic groups. Reported rates of dependence have tended to run higher among White populations than Asian populations, notwithstanding wide variation found within any given ethnic group. Genetic makeup, biology, culture, and environmental exposure combine to produce these gaps, and among the biological contributors, genetically driven differences in how alcohol gets metabolized stand out as especially important.

II.BIOLOGY OF ALCOHOL METABOLISM

The liver is the main site of alcohol metabolism, with only a minor contribution from the stomach and other tissues. The rate at which ethanol is cleared influences blood alcohol concentration, the duration of intoxication, the risk of toxic injury, and the likelihood of developing AUD (1). Although environment and behavior strongly shape drinking patterns, inherited variation in alcohol-metabolizing enzymes remains a major biological determinant of alcohol use and dependence. Under normal conditions, the liver oxidizes about 90–95% of ingested ethanol, whereas 5–10% is eliminated unchanged in breath, urine, and sweat (2). Most ethanol is metabolized through two sequential enzymatic steps. Alcohol dehydrogenase first converts ethanol into acetaldehyde, a highly reactive and toxic compound responsible for many unpleasant effects of drinking, including flushing, nausea, vomiting, headache, tachycardia, hypotension, and general malaise. Because acetaldehyde is cytotoxic and carcinogenic, rapid clearance is essential to limit oxidative stress and tissue damage. Aldehyde dehydrogenase, particularly the mitochondrial isoform ALDH2, then converts acetaldehyde into acetate, a much less harmful molecule. Acetate can subsequently enter central energy metabolism and be converted into carbon dioxide, water, and cellular energy (3). In short, both the overall rate of alcohol elimination and the degree of acetaldehyde accumulation depend on the balance between ethanol oxidation by ADH and acetaldehyde clearance by ALDH.

A second metabolic route exists alongside the ADH–ALDH sequence, and it matters more once drinking becomes heavy or goes on for a long time. Cytochrome P450 2E1, an enzyme that gives this backup system known as the microsomal ethanol-oxidizing pathway its name, becomes more active as alcohol levels climb or exposure persists. Ongoing drinking causes the body to produce more of this enzyme, since its expression can be induced. Faster ethanol clearance is the upside of that adjustment, but there is a cost: more reactive oxygen species get generated, which drives oxidative stress, damages lipids, sparks inflammation, and harms liver cells. That is part of why heightened activity of this pathway is tied to the progression of liver disease linked to alcohol starting with fat buildup, then hepatitis, then fibrosis, and cirrhosis in the worst cases.

Genetic variation among the alcohol-metabolizing enzymes can meaningfully steer both how people drink and their odds of developing AUD, since ADH and ALDH variants change enzyme activity and, with it, the pace of ethanol oxidation and acetaldehyde clearance. Someone who builds up acetaldehyde quickly, or clears it slowly, usually feels worse after drinking and that discomfort can blunt alcohol's appeal and work against dependence forming. The opposite pattern sluggish ethanol oxidation, or acetaldehyde removed efficiently tends to spare a person for those immediate unpleasant effects, which can leave the door open to heavier drinking (4).

III.ADH GENE VARIANTS

Seven closely related genes make up the ADH family on chromosome 4 ADH1A, ADH1B, ADH1C, ADH4, ADH5, ADH6, and ADH7 each coding for an enzyme with its own catalytic profile and tissue-specific pattern of expression. Among them, ADH1B carries the strongest and most consistent link to alcohol dependence, a link borne out both in candidate-gene work and in genome-wide studies (5). One of the best-studied variants, ADH1B*2, codes for an enzyme far more catalytically active than the common ADH1B1 form, so people who carry it turn ethanol into acetaldehyde unusually fast, producing a short-lived spike in acetaldehyde levels after drinking. The result flushing, nausea, palpitations, dizziness, general unease discourages continued or heavy alcohol use, which is why this allele counts among the sturdiest known genetic shields against dependence. A related variant, ADH1C*1, also boosts enzymatic activity relative to its counterpart ADH1C*2, though its protective effect falls short of what ADH1B variants provide. Because how common these alleles differ sharply by population, genetic diversity itself helps account for why susceptibility to alcohol-related disease varies globally (6).

IV.ALDH GENE VARIANTS

ALDH2 provides the mitochondrial enzyme responsible for clearing most of the acetaldehyde left over once ethanol has been processed. Its ALDH2*2 variant stands out clinically above the rest: a single change in one amino acid cuts the enzyme's activity sharply, leaving acetaldehyde around longer than it should be. This variant shows up with real frequency among East Asian populations it is common, for instance, in people whose ancestry traces to China, Japan, or Korea while remaining uncommon among Europeans or Africans. Carrying just one copy is usually enough to noticeably weaken ALDH activity, and it can bring on flushing after even a small amount of alcohol, along with nausea, vomiting, headache, dizziness, a racing heart, low blood pressure, and warmth. With two copies, functional ALDH2 activity is nearly absent, and reactions can be severe enough to make routine drinking essentially impossible which is why these variant ranks among nature's strongest safeguards against dependence on the other hand. Across population studies, carriers reliably drink less and develop AUD less often than those without the variant. Still, anyone who keeps drinking heavily despite reduced ALDH2 function runs a higher risk of alcohol-linked cancers esophageal squamous cell carcinoma since acetaldehyde exposure over time is carcinogenic. Altogether, what the ADH and ALDH variants reveal is how inherited metabolic differences shape alcohol disposition, color the subjective experience of drinking, and influence overall AUD risk a body of evidence that has sharpened the understanding of addiction biology and that supports precision-medicine thinking, where genetic profiling could someday guide individually tailored prevention and treatment (7).

V.NEUROBIOLOGY OF ALCOHOL USE DISORDER

Fundamentally, AUD functions as a relapsing brain disorder, with sustained alcohol exposure rewiring neurotransmitter systems and the interconnected circuits behind reward, motivation, stress response, learning, memory, and executive function. No single pathway can account for what alcohol does, both a one-off drinking episode and long-term use disturb a wide range of processes across the central nervous system that together give rise to, and then sustain, addictive behavior. A single episode drives up dopamine output in the brain's reward circuitry, particularly along the pathway connecting the midbrain's dopamine-producing region to the nucleus accumbens, and this dopamine surge underlies the pleasure and reinforcement that make another drink more appealing. But dopamine tells only part of the story: GABA, glutamate, serotonin, the brain's own opioid-like peptides, endocannabinoids, acetylcholine, and various neuropeptides all shape the brain's overall response to alcohol (8).

Drinking ramps up inhibitory GABA signaling hence alcohol's sedating, anxiety-easing, coordination-impairing effects while at the same time damping down excitatory glutamate signaling, largely by blocking NMDA receptors, which is what disrupts thinking, memory formation, and motor coordination. Between the two, brain activity tilts toward inhibition overall, which accounts for most of what alcohol does acutely to behavior and cognition. Keep drinking over time, though, and the brain begins compensating to restore balance: GABA receptors grow less responsive while glutamate signaling ramps up via more numerous and more active NMDA receptors. Tolerance is the practical result it takes progressively more alcohol to feel the same effect. Stop drinking suddenly, and the compensations that had been masked come rushing to the surface: unchecked glutamate activity paired with weak inhibition can bring on anxiety, tremors, sleeplessness, autonomic instability, seizures, and, at the extreme, delirium tremens. These same adaptations help explain relapse too, since going back to drinking can temporarily quiet withdrawal discomfort and negative mood (9).

More than one neurotransmitter system feeds into dependence. Sustained drinking can disrupt serotonin signaling, which carries consequences for mood, impulsivity, and behavioral control. The body's internal opioid system μ-opioid receptors contribute to alcohol's reward value partly by adjusting how much dopamine gets released along the reward pathway, which is the underlying reason opioid-blocking drugs like naltrexone can ease craving and blunt alcohol's reinforcing pull. Reward, stress regulation, and emotional processing likewise draw in the endocannabinoid system, positioning it yet another candidate for drug development (10).

Once drinking moves from occasional to dependent, stress mechanisms start pulling as much weight as reward circuitry does. Sustained alcohol exposure switches on the extended amygdala and knocks the body's central stress axis spanning hypothalamus, pituitary, and adrenal gland out of its normal balance, raising levels of stress-linked neuropeptides such as corticotropin-releasing factor. During withdrawal, these adaptations show up as anxiety, low mood, and heightened stress reactivity, and they can shift what motivates drinking from chasing a pleasurable high toward simply escaping discomfort, a move from positive to negative reinforcement. Long-term exposure also physically alters several connected brain regions. The region behind planning, impulse control, and decision-making can lose grey matter and show weaker connectivity, undermining self-control, judgment, and the ability to push back against alcohol-related triggers. Elsewhere, greater amygdala reactivity paired with altered hippocampal function can distort emotional processing, learning, and memory including memories specifically tied to drinking situations while changes to the brain reward-related structures can further cement compulsive, cue-triggered alcohol seeking (11). Neuroimmune involvement in AUD has also drawn growing interest: sustained drinking activates microglia and drives up pro-inflammatory

cytokine signaling, which may damage neurons, blunt neuroplasticity, hurt cognition, and raise relapse risk. Shifts in gut bacteria and in how permeable the gut lining becomes may add yet another layer, allowing inflammatory signals originating outside the brain to reach it via immune, hormonal, and neural pathways. Collectively, this evidence pushes addiction models beyond a simple story of neurotransmitter imbalance, marking inflammation and peripheral immune activity as plausible new treatment targets. In brief, AUD emerges from the interplay of reward networks, stress systems, executive-control circuitry, immune processes, and organs beyond the brain, with gradual neuroadaptation reshaping motivation, emotional regulation, and cognitive control as drinking shifts from voluntary to compulsive. This mechanistic picture underlies existing pharmacological treatments and continues to guide the search for therapies that improve recovery and reduce relapse (12).

VI.CLINICAL MANAGEMENT OF ALCOHOL WITHDRAWAL

A period of heavy drinking followed by sudden cessation can bring withdrawal anxiety, tremors, nausea, and insomnia at the milder end, seizures, or delirium tremens at the severe end . Some withdrawal symptoms show up in as many as half of those with an alcohol-related disorder once they quit, though formal, medically supervised detox is needed by only a fraction of them, and many people manage to scale back drinking on their own without any clinical intervention (13).

Whether withdrawal is managed at home or in a hospital comes down to how severe it looks. In milder cases, simple observation paired with supportive measures fluids, correcting electrolytes, thiamine (vitamin B1) may be all that is needed. When medication becomes necessary, the benzodiazepine class carries most of the treatment burden for withdrawal syndrome: diazepam, chlordiazepoxide, lorazepam, oxazepam, and midazolam are the drugs typically used. By strengthening signaling through GABA-A receptors, this drug class eases how severe withdrawal feels and reduces the chances of both seizures and delirium tremens, which is why it is considered first-line care though because of the risk of misuse and overdose, outpatient use calls for careful supervision. Clonidine (working through alpha-2 receptors) and atenolol (a beta-blocker) can be added when autonomic symptoms don't settle down, but neither should they stand alone as treatment, since on their own they neither block severe withdrawal nor reveal symptoms clinicians need to track. Managing withdrawal, then, functions as an entry point the first step toward a longer program combining medication and psychosocial support aimed at abstinence or reduced drinking (14).

VII.PHARMACOLOGICAL TREATMENT OF ALCOHOL USE DISORDER

Regulatory history singles out three medications as the backbone of FDA and EMEA sanctioned drug treatment for AUD.

VIII. DISULFIRAM

Disulfiram earned a genuine historical first when the FDA approved it for AUD in 1951, making it the earliest medication cleared for this purpose. It works by permanently blocking aldehyde dehydrogenase the enzyme that would ordinarily turn acetaldehyde (itself generated from ethanol) into a far less harmful acetate, so acetaldehyde instead accumulates to toxic levels. There may be some contribution from secondary actions, such as blocking the enzyme dopamine β-hydroxylase, but interference with ALDH remains the central mechanism at work. Drinking while taking disulfiram triggers an unpleasant, acetaldehyde-driven reaction to a racing heart, headache, nausea, vomiting. Since the drug's whole therapeutic logic rests on patients anticipating that unpleasant reaction, how well it works in practice depends heavily on whether patients stick with it and stay motivated (15).

IX. ACAMPROSATE

Acamprosate came next in the pharmacological lineup, first cleared for alcohol dependence in Europe back in 1989 and later making its way to the US, Canada, and Japan. Just how it works is still not fully pinned down, though the evidence points toward an effect on glutamatergic signaling possibly through NMDA receptors that helps rein in the hyperglutamatergic state that shows up during withdrawal. Findings from double-blind randomized trials and the meta-analyses built on them have not always agreed: some report a modest-to-moderate edge over placebo for staying abstinent, while a set of large trials run in the US and Germany came up short of showing any clear benefit. Taken together, the data lean toward acamprosate being most useful for holding onto abstinence and preventing relapse after detox, rather than helping someone actively drinking cut back which is consistent with reserving it for patients who have already achieved abstinence (38). Its most common downside is diarrhea, well ahead of the less frequent nausea, vomiting, abdominal discomfort, headache, and dizziness (16).

X. NALTREXONE

Naltrexone works by blocking opioid receptors, and the FDA cleared it for alcohol dependence in 1994; a once-monthly extended-release injectable version followed in 2006, aimed at helping patients stay consistent with treatment. Its main effect is curbing craving, and it appears especially useful for cutting down episodes of heavy drinking. A few meta-analyses back its capacity to lower relapse into heavy drinking relative to placebo, though the picture is murkier when it comes to supporting complete abstinence (17). Fewer studies have examined the injectable version specifically, but what data is available looks favorable for reducing heavy drinking and craving and for improving day-to-day wellbeing.

XI. ADDITIONAL PHARMACOLOGICAL TREATMENTS APPROVED FOR ALCOHOL USE DISORDERS IN EUROPE

Disulfiram, acamprosate, and naltrexone have all found use in both Europe and the United States, but Europe went further still, clearing a fourth medication nalmefene in 2013; its pharmacology closely parallels naltrexone's action on opioid receptors.

Nalmefene is a full antagonist at μ- and δ-opioid receptors and a partial agonist at κ-opioid receptors. Its adverse-effect profile is broadly similar to that of naltrexone, although nalmefene has a longer half-life. Meta-analytic data indicate that it can reduce the number of heavy-drinking days, and one indirect comparison suggested an advantage over naltrexone; however, the clinical relevance of this potential difference remains uncertain. Additional meta-analytic and simulation-based studies also

support its superiority over placebo in lowering overall alcohol consumption. Its approval in Europe was controversial, and a direct head-to-head trial with naltrexone would help determine whether it offers a meaningful therapeutic benefit. European regulators authorized nalmefene for as-needed use on days when patients anticipate drinking, consistent with earlier findings that targeted naltrexone dosing may also be effective on expected drinking days (18).

Side effects reported with naltrexone include nausea, headache, dizziness, and sleep trouble. Older labeling carried a hepatotoxicity warning, one that stemmed mainly from an early study using a higher dose (300 mg per day) in obese male subjects. Published data at the much lower, FDA-approved 50 mg daily dose used for AUD have not shown serious liver damage, though a handful of trials and post-marketing reports have picked up brief, symptom-free increases in liver enzyme levels. Given that history, clinicians should proceed carefully when prescribing naltrexone to someone with active liver disease, and it should not be used at all in cases of acute hepatitis or liver failure (19).

Baclofen was initially developed to treat muscle spasticity through GABA-B receptor agonism before receiving formal approval for AUD in France in 2018, after more than a decade of off-label use in France, other European countries, and Australia. It may reduce the craving and excessive drinking triggered by an initial "priming" drink. Overall, clinical trials, systematic reviews, and meta-analyses have produced mixed results, although baclofen may be particularly useful in patients with coexisting liver disease. Interindividual variability in drug metabolism may partly explain differences in treatment response. Optimal dosing remains debated, and current international guidance recommends individualized dose adjustment based on safety, tolerability, and clinical benefit (20).

There is a particularly convincing case for expanding the medication toolkit for patients whose AUD coexists with mood disorders, anxiety disorders, suicidal ideation, or other substance-use problems, since these overlapping conditions tend to make the addiction more severe and harder to treat. It's also worth flagging that medication tends to work better paired with behavioral therapy notably, the Phase 2 and Phase 3 trials behind the drugs discussed built in brief psychosocial components alongside the medication itself.

XII.BEHAVIORAL/PSYCHOLOGICAL TREATMENTS FOR ALCOHOL USE DISORDERS

Psychological and behavioral treatment options for AUD span a wide range, and quite a few have shown real benefit for either staying abstinent or drinking less. Brief interventions stand out as having some of the sturdiest evidence behind them, and twelve-step facilitation which links patients up with mutual-help groups has proven its worth too.

Systematic reviews and pooled meta-analytic data back the effectiveness of brief interventions for AUD, motivational-interviewing-based ones especially. Mindfulness and acceptance-based methods have also picked up steam; rather than zeroing in on correcting distorted thought patterns, they change how a person relates to their own symptoms and present-moment experience. Typical strategies involve keeping track of alcohol intake, spotting situations that carry elevated risk, and building the practical skills needed to get through moments when drinking feels likely. Cognitive-behavioral treatment can be one-on-one, in a group, or adapted to work with couples or whole families (21).

Acceptance- and mindfulness-based methods now appear across a range of treatment settings and delivery formats, brief interventions among them, and the supporting evidence suggests real promise. At their core are present-moment awareness, a stance of non-judgment toward oneself and others, and a greater willingness to accept whatever one is currently experiencing; group delivery is typical, though individual sessions are an option too.

Computer-, web-, and phone-based digital programs have started weaving together ideas from brief intervention, CBT, mindfulness, and mutual-help traditions, and a number of these have posted encouraging results in early testing. A case in point is the computerized program built by the U.S. federal alcohol research institute, nicknamed 'Take Control,' which blends motivational-interviewing elements with skills-based coping training; the goal was to offer psychosocial backing especially to patients randomized to placebo — while keeping people engaged and adherent within pharmacotherapy studies (22). Separately, taking part in mutual-help groups has been tied to AUD recovery even among people who never get any formal treatment at all.

Reading too much into mutual-help outcomes is risky because of self-selection: people who choose to join tend to already be more motivated to change, which muddies any attempt to isolate what part of group participation is driving the benefit. These groups also widen a person's social support network in ways that reinforce staying abstinent or cutting back, so both personal motivation and supportive relationships probably play a part in the outcomes seen.

XIII.RECENT DEVELOPMENTS IN PHARMACOLOGICAL AND BEHAVIORAL APPROACHES

The more researchers learn about AUD including which patient traits, predict how well someone will respond to existing treatments the more translational work moves forward toward new therapies. Advances across neuroscience, genetics, and biology keep expanding the list of candidate targets for interventions that are both novel and personalized. Pharmacological research historically leaned heavily on reward and positive-reinforcement circuitry the dopamine, opioid, and glutamate systems above all since these mechanisms drive much of alcohol's early appeal; naltrexone and acamprosate both traces back to this line of thinking and deliver reductions in craving or relapse that, while modest, still matter clinically. Even so, many patients still struggle to achieve lasting recovery, which points to a need to look at mechanisms beyond these established ones. Systems tied to stress are getting more attention as important drivers behind the shift toward compulsive drinking and relapses. Long-term alcohol exposure can throw off the body's central stress axis and recruit stress-linked systems built around corticotropin-releasing factor, dynorphin, and norepinephrine effects that stand out most clearly during withdrawal and extended abstinence, when anxiety, low mood, and stress sensitivity can pull someone back toward drinking through negative reinforcement. That has driven interest in agents that target CRF receptors, kappa-opioid receptors, and adrenergic signaling, though it is still too early to say how useful these will prove clinically (23).

AUD is now often framed as a condition spanning multiple body systems, sustained by ongoing back-and-forth between the brain and organs elsewhere in the body a framing that captures how the nervous system, immune system, gut, and liver all interact, and one that has widened the search for workable treatment mechanisms. Inflammation, both in the brain and beyond it, ranks

among the most actively studied of these angles : ongoing alcohol exposure can activate immune pathways outside the brain along with inflammatory signaling within it, spur cytokine release and microglial activation, disrupt how neurons function, and interfere with neuroplasticity all of which has been linked to craving, cognitive trouble, mood problems, and a greater chance of relapse. That has pushed researchers to evaluate anti-inflammatory compounds, immune-modulating drugs, and other approaches meant to quiet neuroinflammatory signaling as add-on treatments (24).

Interest has also turned toward the connections linking gut, liver, and brain. Heavy drinking can throw the gut's bacterial balance off and weaken the intestinal lining, which lets bacterial toxins slip into the bloodstream and set off inflammation throughout the body signals capable of disrupting liver function and reaching the brain by immune, hormonal, and nervous-system routes. Disrupted gut bacteria have been linked to changes in stress reactivity, emotional regulation, cognitive performance, and alcohol-seeking behavior, prompting researchers to test probiotics, prebiotics, dietary changes, and fecal microbiota transplants as add-ons to standard treatment. Meanwhile, work in genetics, epigenetics, and biomarker discovery is steadily nudging AUD care toward greater personalization: genetic differences can affect disease risk, treatment response, and how likely relapse is, while alcohol itself can trigger heritable changes to gene activity that do not touch the DNA sequence directly. Biomarkers built from genetic, inflammatory, metabolic, or brain-imaging data could eventually help clinicians match each patient to the intervention most likely to work. Behavioral care remains foundational throughout approaches such as structured cognitive-behavioral work, motivational counseling, reward-based contingency management, and relapse-prevention training grounded in mindfulness all show measurable benefit. Digital health tools apps, telehealth, real-time ecological momentary assessment, wearable sensors, and AI-assisted programs are widening access to care and enabling more continuous tracking of drinking, craving, and relapse risk, which may in turn strengthen adherence and open the door to earlier intervention for those at greatest risk.

Together, these advances suggest that future AUD treatment will increasingly rely on multimodal strategies that combine medications targeting multiple biological systems with evidence-based behavioral therapies. As the interactions among brain circuits, immune signaling, peripheral organs, and psychosocial factors become better understood, precision-medicine approaches may offer more effective and durable recovery.

XIV.CONCLUSION

AUD is best understood as a chronic, multifactorial disorder shaped by genetic vulnerability, neurobiological adaptation, psychological factors, and environmental context. Variants in alcohol-metabolizing enzymes, particularly ADH and ALDH, help explain differences in alcohol sensitivity and AUD risk across individuals and populations. Repeated alcohol exposure alters neurotransmitter systems and neural circuits involved in reward, stress regulation, and executive control, thereby promoting dependence and relapse. Effective management therefore requires an integrated, multidisciplinary strategy combining appropriate withdrawal care, evidence-based pharmacotherapy, and behavioral support. Although major advances have clarified the biology of AUD and expanded therapeutic options, important questions remain, including why clinical presentation varies so widely, why some individuals recover without formal treatment, and how interventions can be better tailored to each patient. Continued research into genetics, neurobiology, and emerging pharmacological targets will be essential to improve prevention, treatment, and long-term recovery.

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