Review

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Review

Current Pharmacotherapies for Alcohol Use Disorder in Italy: From Neurobiological Targets to Clinical Practice

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Abstract: Alcohol Use Disorder (AUD) is a global social burden, with alcohol being the most prevalent psychoactive substance used by older individuals. Alcohol intake is a recognized carcinogen and is regulated by alcohol dehydrogenases (ADHs) and aldehyde dehydrogenases (ALDHs), with activity and expression determined by genetic factors. Alcohol withdrawal challenges include tremors, diaphoresis, anxiety, sleeplessness, hallucinations, and convulsions. Alcohol also stimulates cholinergic interneurons and increases the sensitivity of 5-HT3 receptors within the nucleus accumbens, which play a critical role in reward and addiction. Chronic alcohol consumption alters the mesolimbic dopaminergic system, an important neural pathway involved in reward processing. First-line pharmacotherapies for AUD include oral naltrexone and acamprosate, disulfiram, and nalmefene. Off-label therapies include baclofen, topiramate, gabapentin, ondansetron, and cytisine. Understanding altered neuronal signaling pathways by alcohol helps identify effectors involved in mitigating central actions and offers new therapeutic perspectives for alcohol addiction rehabilitation.

Keywords: addiction; alcohol use disorder; anticraving; off-label

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1. Introduction

Alcohol Use Disorder (AUD) is the most prevalent of all substance use disorders, and it constitutes a worldwide social and economic burden [1]. In the U.S., alcohol consumption is the main psychoactive substance among older individuals, and the excessive and chronic use, including binge drinking, is increasing for recreational purposes, particularly among females [2]. In Europe the pictures are worst, with alcohol responsible for about 6.5% of all deaths (11.0% among men and 0.8% among women) and 11.6% of all disability-adjusted life years DALYs (17.3% for men and 4.4% for women), making it the region with the highest alcohol-attributable burden globally [3]. Alcohol intake is a well-established risk factor for developing injuries, non-communicable diseases, and multiple types of cancer. In 2018, around 23,300 early cancer fatalities in Europe were linked to alcohol consumption, with colorectal, liver, pancreatic, and esophageal cancers representing the highest incidence among males, and breast cancer among females [4].

Alcohol metabolism is governed by alcohol dehydrogenases (ADHs) and aldehyde dehydrogenases (ALDHs), whose activity and expression are determined by genetic factors. The polymorphisms of the ADH1B, ADH1C, and ALDH2 genes affect the regulation of acetaldehyde

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metabolism and the likelihood of alcohol consumption [5]. CYP2E1 and other cytochrome P450 isozymes play important and complementary roles in the metabolism of alcohol substrates [6]. Acetaldehyde, a product of ethanol metabolism, is not a simple metabolite of alcohol, but a toxic agent with deleterious effects on cellular metabolism and potentially carcinogenic [7]. It can cause significant cellular and tissue damage, particularly through mitochondrial dysfunction and the accumulation of reactive oxygen species (ROS), further damaging cell structures. Acetaldehyde is also recognized as a carcinogen capable of forming adducts with DNA, which are stable covalent bonds that can interfere with the replication and transcription of genetic material, increasing the risk of mutations [8].

Alcohol activates γ-aminobutyric acid type A (GABAa) and glycine receptors, which are the main receptors that inhibit signals in the central nervous system of vertebrates [9]. Chronic use of alcohol decreases the sensitivity and downregulates the expression of these inhibitory receptors while upregulating the Central Nervous System excitatory Kainate receptors (KA-Rs) that include N-methyl-D-aspartate (NMDA) receptors [10–12]. Alcohol withdrawal results in insufficient inhibition, triggering activation of the lateral habenula (LHb) and neuronal hyperactivity, which can induce severe clinical manifestations, including tremors, diaphoresis, anxiety, sleeplessness, hallucinations, and convulsions, potentially culminating in delirium tremens [10,13,14]. Furthermore, alcohol stimulates cholinergic interneurons (CIN) and increases the sensitivity of 5-HT3 receptors within the shell region of the nucleus accumbens (NAcSh), which play a critical role in reward and addiction [15]. Chronic alcohol consumption markedly alters the mesolimbic dopaminergic system, an important neural pathway involved in reward processing [16]. This pathway involves the alcohol-induced secretion of β-endorphins, which bind to mu-opioid receptors (MORs) on GABAergic interneurons inside the ventral tegmental area (VTA). Activation of MORs inhibits these interneurons, resulting in a reduction in the GABA-mediated inhibitory action on dopaminergic neurons [17]. This disinhibition increases dopamine release in the nucleus accumbens and enhances dopaminergic activation, hence reinforcing alcohol-related behaviors and facilitating the beginning of dependence [18,19]. In Figure 1 is schematically represented the mechanism of action of the main therapeutic drugs approved for alcohol dependence.

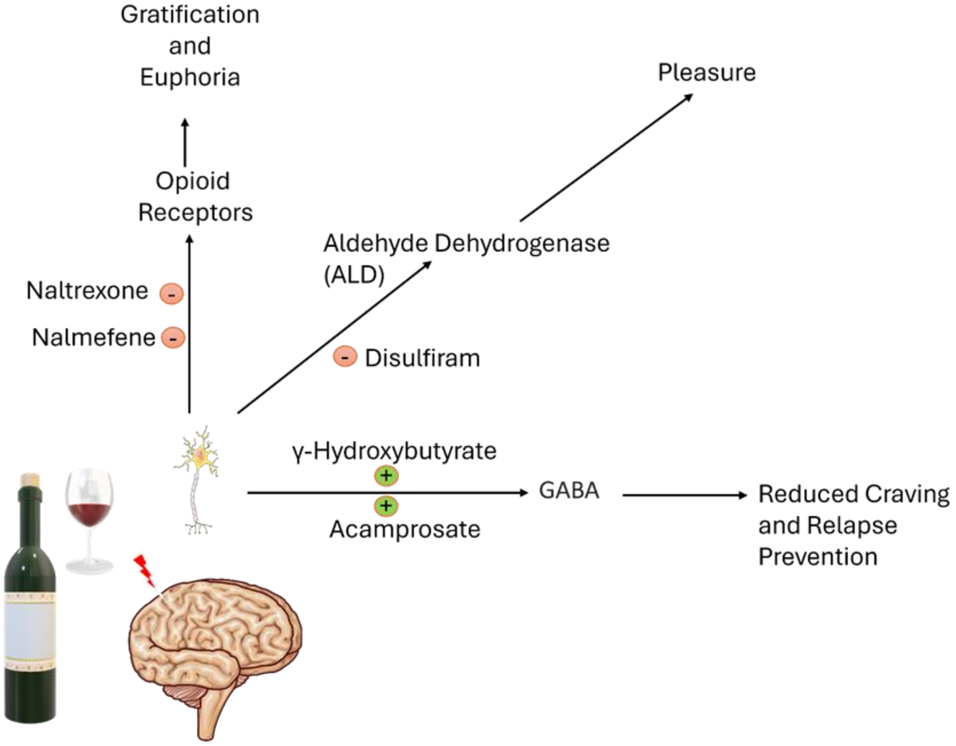

Figure 1. Mechanism of action of the main therapeutic drugs for alcohol dependence.

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Cessation of alcohol intake causes an increase in craving, which can be categorized, based on the Clinical Theorist's Questionnaire (CTQ), into three primary subtypes: reward craving, relief craving, and obsessive craving [20]. Reward craving, indicating the desire for the pleasurable effects of alcohol, is linked to the dopaminergic mesolimbic system [21]. Relief craving is motivated by the desire to diminish adverse emotional experiences, involving the GABAergic and endogenous opioid systems [22]. Obsessive craving, linked to habit circuits in the dorsal striatum, is characterized by intrusive thoughts and compulsive urges to consume alcohol [23].

Given the significant health and economic burden of alcohol use and its clinical management, it is essential to provide an evidence-based review of the current pharmacological treatment, to identify their mechanisms of action, efficacy, and pharmacological uses.

This narrative review aims to provide a comprehensive perspective supporting a more informed clinical approach to assessment and treatment in Italy.

2. Pharmacotherapies and Anti-Craving Therapy for AUD

The first-line pharmacotherapies for alcohol use disorder are oral naltrexone and acamprosate [24]; these are the only two therapies approved by the US Food and Drug Administration [25]. In Italy, the treatment of alcoholism is recognized as a social disease (Law 125/2001) and is included among the LEAs (DPCM 12 January 2017): regions must guarantee free access to diagnosis, medication, psychotherapy and rehabilitation. Apart from naltrexone and acamprosate here there are other therapies approved for alcohol dependence: disulfiram, nalmefene and sodium oxybate (https://www.aifa.gov.it).

2.1. Naltrexone

Naltrexone is an opioid antagonist of MOR, Delta-Opioid Receptor (DOR), and Kappa-Opioid Receptor (KOR), at first used for substance use disorder, in particular for opioid addiction, currently has been shown to have efficacy in the treatment of alcohol use disorder [26]. Naltrexone is structurally derived from the morphinan family and features a cyclopropylmethyl group linked to a hexahydro-methanobenzofuroisoquinoline core. The molecule contains two hydroxyl groups, optimally located to improve receptor binding affinity [27]. 6-β-naltrexol is the principal metabolite of naltrexone in humans, whereas 2-hydroxy-3-O-methylnaltrexol is a secondary metabolite [28]. The pharmacokinetics of naltrexone indicate that after oral administration, the drug is effectively absorbed by the gastrointestinal tract and is proficiently metabolized by the liver; the mean time to peak plasma concentration (Tmax) is roughly 1 hour. The maximum plasma concentration (Cmax) and area under the curve (AUC) of the principal active metabolite, 6β-naltrexol, exceed those of the parent drug. 6β-Naltrexol exhibits prolonged systemic persistence and considerably enhances overall pharmacological efficacy. The observed elimination half-lives (T1/2) of naltrexone and 6β-naltrexol are comparable and stay consistent across extended administration, despite significant interindividual heterogeneity and among individuals with cirrhosis and other severities of liver disease [28–30]. Naltrexone reduces craving by blocking the enhancement of endorphin levels [31]. There are three naltrexone forms: 50 mg/d oral, 100 mg/d oral, and injection. In a risk-benefit analysis, naltrexone, 50 mg/d oral, is the best form of naltrexone therapy. Additional studies have shown the superiority of naltrexone over acamprosate in subjects with severe AUD, particularly among clinical profiles characterized by high reward craving and propensity for relapse into heavy drinking [24,32].

2.2. Acamprosate

Acamprosate is an acetylated form of taurine with a structural analogy to GABA and many other amino acids [33,34]. Acamprosate exhibits low oral bioavailability (~11%) attributed to inadequate gastrointestinal absorption, with food further diminishing systemic exposure. It maintains linear pharmacokinetics within therapeutic ranges, with distribution limited to extracellular fluid, characterized by a low volume of distribution (~0.6 L/kg) and minimal plasma protein binding.

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Acamprosate is not metabolized by the liver and is excreted unchanged by the kidneys, with renal clearance very similar to the glomerular filtration rate [35]. The mechanism of action of acamprosate is still unclear. The evidence suggests that multimodal effects, mainly the action on the NMDA receptor, play a central role [34]. A preclinical study has shown decreases in postsynaptic potentials in the rat neocortex after it was administered. Acamprosate's daily dose is 1.3 or 2 g in 3 divided administrations [36]. This dosage depends on the complex pharmacokinetics of this drug, and the absorption and elimination of acamprosate are not fully recognized. Recent studies explore possible alternative dosing strategies to improve treatment adherence [24,34,37]. The American Psychiatric Association (APA) practice guideline suggests that acamprosate be offered to patients with moderate to severe AUD who aim to reduce alcohol consumption or reach abstinence [25,37].

2.3. Disulfiram

Disulfiram is the first drug approved for alcohol use disorder, It is a quaternary ammonium compound characterized by strong electrophilic properties, which significantly influence its chemical reactivity and biological interactions [38]. Disulfiram is not an anti-craving drug; it acts as an aversive agent. The main action for maintaining alcohol abstinence is psychological [39]. Disulfiram irreversibly inhibits the enzyme aldehyde dehydrogenase, accumulating acetaldehyde that causes tachycardia, flushing, nausea, and vomiting [40]. Disulfiram dosage is between 250 and 500 mg/day [41]. Disulfiram is an efficacious treatment compared to anticraving pharmacological therapies [39]. The research suggests that disulfiram should be administered continuously under supervision and alongside supportive psychotherapy to increase its effectiveness; in these instances, it is not inferior to conventional oral therapies [42,43].

2.4. Nalmefene

Nalmefene is the most recent treatment of AUD approved by the European Medicines Agency to decrease alcohol use and binge drinking in patients with AUD [44]. Nalmefene is an opiate derivative with a chemical similarity to naltrexone (6-methylene-naltrexone); it acts like a MOR and DOR antagonist and a partial KOR agonist [45]. Preclinical studies indicate that nalmefene is quickly absorbed, reaching its highest level in the blood (Tmax) in about 0.35 hours, with a peak concentration (Cmax) of 12.24 ng/mL. It takes about 10.7 hours for half of the drug to be eliminated from the body, and when taken by mouth, only 41% of it is available in the system. It has an elimination half-life (t1/2) of approximately 10.7 hours and an oral bioavailability of 41%, indicating its modest systemic availability after oral dosing [46]. Nalmefene has a different mechanism of action from that of its extensive competitor. The dosage of nalmefene is 18 mg as needed, although in many trials it is administered once a day [47]. In a paper, the expert opinion underlines that nalmefene has substantial advantages over naltrexone in the treatment of AUD [48].

2.5. Sodium Oxybate

Sodium oxybate or γ-hydroxybutyrate (GHB) is an endogenous short-chain fatty acid synthesized in the nervous system [49]. Sodium oxybate exhibits linear and dose-proportional pharmacokinetics, characterized by fast absorption (Tmax 30–75 minutes), a quick elimination half-life (0.5–1 hour), and no significant accumulation upon repeated dosage, hence endorsing a reliable profile for chronic administration [50]. Sodium Oxybate is approved for the treatment of Alcohol withdrawal syndrome and in the treatment of AUD, has a particular mechanism. Sodium oxybate acts on $GABA_B$ receptors and extrasynaptic $GABA_A$ receptors, resulting in alcohol-mimetic effects [51]. Most studies on sodium oxybate use a dosage of 50 mg/kg divided into three administrations per day [52]. Sodium oxybate was at least as effective as benzodiazepines in patients with alcohol withdrawal syndrome, rapidly alleviating symptoms, and was at least as effective as other anti-craving drugs in maintaining abstinence in alcohol use disorder, but inexact dosing or illicit sodium oxybate use has an increased risk of overdose [53].

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The pharmacological agents currently approved in Italy for the treatment of AUD were summarized in Table 1, highlighting their mechanisms of action and principal clinical effects.

Table 1. Approved drugs for AUD: targets and main clinical effects.

Drug	Signaling	Clinical Effect
Naltrexone	Antagonist of **MOR, DOR, KOR** opioid receptors	Reduces **craving** and **heavy drinking**, superior in high-relapse profiles
Acamprosate	Unclear; likely **modulates NMDA** receptors and GABA analog	Supports **abstinence**, especially in **moderate to severe AUD**
Disulfiram	**Aldehyde dehydrogenase inhibitor**; aversive agent	Maintains abstinence via **psychological deterrent**
Nalmefene	**MOR/DOR antagonist**, **KOR partial agonist**	Reduces **alcohol use and binge drinking**, effective
Sodium Oxybate	**$GABA_B$ agonist**, acts also on **extrasynaptic $GABA_A$**	Effective in **withdrawal** and **abstinence maintenance**, mimics alcohol effects

3. The Off-Label Therapy

Despite the availability of approved treatments for AUD, various off-label medications are also used to expand therapeutic options, including some of the most adopted in clinical practice.

3.1. Baclofen

Baclofen is a promising drug approved for muscle spasticity. Baclofen is a lipophilic derivative of GABA with a highly selective agonist action on the γ-aminobutyric acid B ($GABA_B$) receptor [54,55]. Baclofen has fast oral absorption (Tmax 1–2 hours), a short half-life (2–6 hours), and is mainly eliminated by renal excretion, with linear pharmacokinetics facilitating predictable exposure over chronic treatment [56]. Baclofen inhibits the release of excitatory neurotransmitters, particularly in the mesolimbic systems, acting on $GABA_B$ receptors, which are numerous in the limbic system [57,58]. Baclofen dosage for AUD treatment is 5 mg three times per day for 3 days, then increasing the dose until 10 mg three times per day for 27 days [59]. Baclofen shows better abstinence rates than placebo, but not in other outcomes like craving or decreasing heavy drinking [57].

3.2. Topiramate

Topiramate is a sulfamate-containing compound approved for epilepsy [60,61]. Topiramate exhibits linear pharmacokinetics over the 100–800 mg dose range, with an oral bioavailability of 81–95%, unaffected by food intake. It has a low oral clearance (22–36 mL/min) and a prolonged elimination half-life of approximately 19–25 hours, primarily eliminated unchanged via renal excretion [62]. Topiramate is a promising drug for AUD, but its mechanism of action is still unclear; it seems to act on GABA receptors and, in animal studies, blocks the effects of kainite-induced excitatory conductance and increases the activation of postsynaptic NMDA receptors [63,64]. Some clinical studies indicate that the dosage of topiramate most efficient for treating AUD is 300 mg/day [65,66]. The topiramate efficacy is questionable; it seems to reduce the abstinence syndrome but does not reach the abstinence [55,67].

3.3. Gabapentin

Gabapentin is a gamma-aminobutyric acid analog, which is an effective antiepileptic and is also finding its use in AUD [68]. Gabapentin displays dose-dependent pharmacokinetics due to saturable absorption, with a half-life of 5–7 hours and renal elimination in unchanged form [69]. The pharmacological actions of gabapentin are not fully understood; it increases the GABA concentration [70]. Gabapentin dosage is between 600 and 1800 mg/day [68,71]. Gabapentin showed good efficacy in reducing cravings and withdrawal symptoms [71,72].

Pregabalin is structurally like gabapentin and the mechanism of action is the same, but it has a higher degree of oral absorption that is linear with the dose. A clinical study reports the efficacy and safety of pregabalin treatment of AUD in doses up to 600 mg per day [72].

3.4. Ondansetron

Ondansetron is a selective 5-HT3 receptor antagonist, it is approved as an antiemetic for cancer treatment-induced and anesthesia-related nausea and vomiting [73]. Ondansetron shows linear pharmacokinetics with a short elimination half-life of approximately 1.6 to 1.9 hours and is primarily excreted unchanged by the kidneys [74].There have been studies since the early 2000s about the use of ondansetron to decrease drinking in patients with AUD [75,76]. The dosage of ondansetron is 4 mcg/kg twice daily for 8 weeks [76]. Ondansetron is an effective drug in AUD patients, presumably for the action on serotoninergic systems, but has no efficacy in treating AUD patients with no comorbid with Major Depressive Disorder (MDD) [75,77].

3.5. Cytisine

Cytisine is a natural alkaloid extracted from plants of the Faboideae subfamily, It was used for the pharmacological treatment of tobacco use disorder [78]. Cytisine is rapidly absorbed, reaching peak plasma concentrations in approximately 1.3 hours. It shows a relatively short elimination half-life of about 4.8 hours, with a maximum concentration around 12.1 nanograms per milliliter and an overall exposure (AUC) of 49.5 nanogram-hours per milliliter. Cytisine is primarily eliminated unchanged in the urine, with no detectable metabolites found in plasma or urine [79]. Cytisine has a high affinity for $\alpha4\beta2$ and $\alpha7$ nAChRs, these receptors acting on the reward system. The anticraving effect of cytisine is attributed to its partial agonist activity at $\alpha4\beta2$ nicotinic acetylcholine receptors. cytisine is safe and effective for smoking cessation and shows a potential role in reducing alcohol self-administration in smokers, while various therapeutic regimens have been established for smoking cessation, there is currently no standardized dosing protocol for cytisine in the context of AUD treatment [78,80].

Table 2 summarizes the principal off-label pharmacological agents currently employed in clinical practice in Italy for the management AUD, highlighting their proposed mechanisms of action and reported clinical benefits based on available evidence.

Table 2. Principal off-label medications employed in Italy for AUD: mechanisms of action and clinical effect.

Drug	Signaling	Clinical Effect
Baclofen	Selective **$GABA_B$ receptor agonist**	Improves **abstinence**, not effective for craving or heavy drinking
Topiramate	Modulates **GABA and glutamate (NMDA/kainate)** receptors	Reduces **withdrawal symptoms**, limited effect on abstinence
Gabapentin	Increases **GABA** levels	Reduces **craving** and **withdrawal symptoms**
Pregabalin	Binds **$\alpha2\delta$ subunit of Ca^{2+} channels**	Reduces **craving**, effective and better absorption than gabapentin

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Ondansetron	**5-HT3 receptor antagonist**	Reduces **drinking** in AUD with **comorbid MDD**
Cytisine	**Partial agonist of $\alpha 4\beta 2$ nAChRs**, modulates **dopamine reward system**	Reduces **alcohol self-administration** in **smokers**

4. Conclusions

This review offers a practical guide for clinicians by illustrating the diverse effects of alcohol on the central nervous system, including widespread psychomotor depression, impaired information storage, disrupted logical reasoning, and motor incoordination. Additionally, alcohol's stimulation of the brain's reward system may help explain the development of addiction. This comprehensive perspective supports a more informed clinical approach to assessment and treatment.

Understanding the altered neuronal signaling pathways by alcohol seems helpful in identifying effectors involved in the mitigation of central actions, offering new therapeutic perspectives for alcohol addiction rehabilitation.

Naltrexone and acamprosate show successful results in the realm of AUD treatment. A daily oral dose of 50 mg/day of naltrexone is effective in reducing alcohol cravings. At the same time, acamprosate, acting on the NMDA receptor, is recommended for moderate to severe AUD patients. Disulfiram doesn't act like an anticraving drug, and its effectiveness is related to the psychological mechanism of action.

The European Medicines Agency has approved nalmefene (KOR agonist and MOR antagonist) and sodium oxybate (Agonist $GABA_AR$ and $GABA_BR$). Promising results demonstrate nalmefene is a potential alternative treatment to naltrexone, due to its dual action, and the potential advantages of sodium oxybate Alcohol Withdrawal Syndrome and AUD treatment.

In patients with a concomitant opioid dependence, it should be noted that naltrexone and nalmefene are contraindicated in patients treated with methadone as it could lead to acute withdrawal syndrome and potential physiological decompensation. In this case, a wash-out and confirmation of suspension of the opioid agonist is required before starting the administration of alcohol dependence treatment. At the same time, the administration of either disulfiram or sodium oxybate in association to methadone treatment may lead to increased CNS toxicity. Acamprosate does not affect the opioid system or depress breathing, so it is generally considered safer in patients on methadone therapy.

Among gabaergic drugs, topiramate and gabapentin, already used to treat alcohol withdrawal symptoms, may also be beneficial to facilitate alcohol cessation, sparing benzodiazepine administration.

Despite the existence of approved (on-label) pharmacological therapies for AUD, and the increasing use of off-label strategies, there is still a significant gap in robust evidence on their safety and tolerability in real patients. The latter often present complex clinical pictures, with psychiatric and organic comorbidities and multiple addictions (from opiates, benzodiazepines, stimulants or cannabis), which alter the risk-benefit profile of treatments. In addition, the poor therapeutic adherence and frequent psychosocial instability make the "ideal patient" of traditional clinical trials unrepresentative.

Therefore, it is urgent to design pragmatic and realistic studies that evaluate the efficacy, safety and tolerability of anti-alcohol drugs in highly complex populations, including those on methadone substitution treatment or other concomitant addiction therapies.

To address the complexities of AUD, the strategies of these pharmacotherapies consider the mechanisms of action, dosages, and potential advantages in different patient populations. Ongoing research endeavors aim to refine existing treatments in other countries and introduce novel medications.

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Further studies should be conducted to map emerging trends and future approaches in pharmacological management and develop effective and safe therapeutic algorithms with an integrated and personalized approach in a comprehensive framework.

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Abbreviations

The following abbreviations are used in this manuscript:

AUD	Alcohol Use Disorder
ADHs	Alcohol Dehydrogenases
ALDHs	Aldehyde Dehydrogenases
DALYs	Disability-adjusted life years
ROS	Reactive Oxygen Species
GABA	γ-Aminobutyric Acid
KA-Rs	Kainate Receptors
NMDA	N-methyl-D-aspartate
LHBs	Lateral Habenula
CIN	Cholinergic Interneurons
NAcSh	Nucleus Accumbens
MOR	Mu-Opioid Receptor
VTA	Ventral Tegmental Area
CTQ	Clinical Theorist's Questionnaire
KOR	Kappa-Opioid Receptor
DOR	Delta-Opioid Receptor
GHB	γ-Hydroxybutyrate
MDD	Major Depressive Disorder

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