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ORIGINAL PAPER

Neurochemical Evidence of Preclinical and Clinical Reports on Target-Based Therapy in Alcohol Used Disorder

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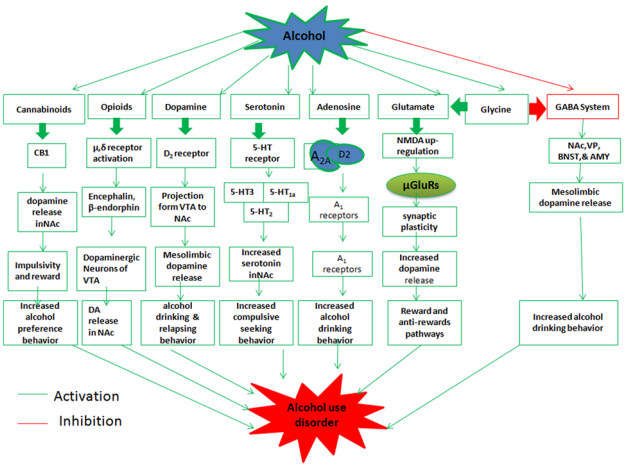
Abstract

Alcohol use disorder (AUD) is a chronic relapsing disorder, which enforces a person to compulsively seek alcohol, restricting control over alcohol intake leads to emergence of an undesired emotional state during abstinence. There are recent advances for better understanding of neurocircuitry involved in the pathophysiology of AUD. Alcohol interaction with neuronal membrane proteins results in changes in neuronal circuits. It is also linked with the potential medication and their clinical validation concerning their pharmacological targets for alcoholic abstinence. This review covers research work from the past few decades on the therapeutic advances on treatment of alcohol dependence; further detailing the fundamental neurochemical mechanisms after alcohol administration. It also covers interaction of alcohol with GABAergic, glutaminergic, dopaminergic, serotonergic and opioid systems. This review further elaborated the neurobiology of noradrenergic, cholinergic and cannabinoid systems and their interaction with AUD. Elaborative information of potential drug targets under current exploration for AUD treatment with their mechanisms are reported here along with clinical outcomes and the associated side effects.

Graphic Abstract



Keywords Alcohol used disorder · GABA · Dopamine · Opioid · Cannabinoids · Serotonin

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Introduction

Around the world, alcoholic beverages are consumed for recreational and ceremonial activity. The moderate use of alcohol is considered to be beneficial for socialization, as a mood elevator, to reduce anxiety [1]. However, chronic consumption of alcohol leads to compulsive alcohol seeking, and when the person is not drinking, there occurs emergence of different emotional conditions [2, 3]. Alcohol use disorder (AUD) causes reward and stress, and insensitive salience, which is mediated by various neurochemical changes [4]. Modulation of neurochemicals can cause severe consequences in the functioning of various brain region of the central nervous system (CNS) [5], and associated metabolic process [6]. Chronic intake of alcohol causes brain damage, characterized by the cerebral and cerebellar atrophy, leading to impaired neuronal function within the hippocampus and frontal cortex [7, 8]. Apart from this, it causes alcohol-specific disorders, such as Wernicke-korsakoff syndrome, hepatic encephalopathy and pellagra. Heavy alcohol consumers exhibit cognitive and motor impairments, cholinergic deficits, and dementia [9]. It is known worldwide that alcohol abuse and misuse is the third-largest leading risk factor for premature death. According to the World Health Organization, about 2.5 million people die each year from alcohol-related causes, i.e., almost 4% of total death is due to AUD, which is greater in number as compared to HIV/AIDS, violence, or tuberculosis [10].

This review has an interior view on the currently available pharmacological therapies, and the major neurochemical mechanism underlying AUD. In the last few decades, researchers have come across various cellular, biochemical and molecular basis linked with AUD. The review focuses on fundamental studies of various neurochemical systems which are linked to different pathways through which any particular drug would reflect their desired pharmacological activity. There are generally two approaches used for the treatment of AUD, i.e., first to gradually reduce alcohol drinking behaviour followed by motivational approach and abstinence. However, a significant reduction in alcohol drinking behaviour improves the health and quality of life [11]. Further, the combination drug therapy and motivational approach were moderately effective for AUD [12, 13]. The review elaborately described the information of the drugs involved in the medication of AUD with a description of the changes in different neurochemical systems by a particular drug. Moreover, the review presents a table, which notifies the approved pharmacological therapies, mechanism of action, clinical reports and the adverse effects of the listed drugs. Additionally, this paper highlighted the novel biochemical and neurochemical marker and drug under trial for AUD. Based on previous pathophysiological evidence and ongoing research, it is concluded that neurochemical target-based therapy can be a better approach for the treatment of AUD.

Target-Based Therapy of AUD and Respective Neurochemical System

GABAergic System and Drugs Acting on it

Gamma-aminobutyric acid (GABA) is considered to be the principal inhibitory neurotransmitter in the brain. Alcohol seeking and drinking can be suppressed by stimulating a $GABA_B$ receptor [14]. Gabapentine mediates its action through $GABA_B$ and facilitates the chloride ions in the Nucleus Accumbens (NAc), ventral palladium (VP), bed nucleus of the stria terminals (BNST), and amygdala (AMY), thereby reducing alcohol-seeking behaviour [15]. Similarly, baclofen, a $GABA_B$ agonist, suppresses alcohol-stimulated dopamine release in the mesolimbic dopamine system and reduces alcohol drinking behaviour [16]. Further, topiramate and acamprosate antagonize the glutamate α-amino-3-hydroxy-5-methyl-4-isoxazole propionic acid (AMPA) receptor and act as modest $GABA_A$ agonists, acting on the calcium-dependent mechanism of alcohol reward and ultimately antagonizing alcohol-induced reward effects [17].

Glycine

The amino acid glycine is prominent in the regulation of emotional states. It causes the suppression of alcohol drinking by acting on the GABAergic systems [18, 19]. Glycine plays a critical role as an inhibitory neurotransmitter in the spinal cord and brain stem [20], but on the other hand, it potentiates the action of glutamate via its co-agonist activity on the N-methyl-D-aspartate (NMDA) receptors. According to recent research, inhibition of glycine transporter (GlyT) in rodents may reduce alcohol consumption [6]. Alcohol causes an increase in the function of the glycine receptor (GlyR) [21].

Adenosine

Adenosine is responsible for suppressing the release of other neurotransmitters in the CNS by modulating neurotransmission. It is known that higher levels of adenosine cause glutamate increase in the brain region. Further, it is known that dimerization of postsynaptic adenosine A_{2A} receptors with dopamine D2 receptors in the striatum influences reward-related behaviour [22, 23]. It is known that alcohol may affect the adenosine receptor coupling [24], resulting in an increase in the activation of adenosine A_1 receptors, which

are responsible for ataxia and the sedative effects of alcohol. Adenosine is also linked with glutamatergic neurotransmission. Thus we can say that adenosine is considered to be strongly involved in alcohol addiction [25].

Glutamatergic System and Drugs Acting on it

Glutamate is responsible for controlling signal transmission and metabolic activities in the brain. Through several research activities, it has been found that NMDA receptor has more affinity for alcohol than AMPA and kainate receptors, which are also modulated by the consumption of alcohol [26]. Chronic alcohol administration produces an adaptive up-regulation of NMDA receptor activity in rodent brains and cultured cells [27]. Thus during withdrawal or relapse, a rebound activation of these receptors occur, playing an important role in the alcohol withdrawal syndrome, including delirium tremors and especially seizures [28, 29]. According to the result of various research works, we concluded that the mechanism of action is to interfere with the phosphorylation and compartmentalization of this receptor [28, 30]. Some drugs like acamprosate (weak NMDA antagonist), zonisamide alter the concentration of γ-glutamyl-transferase, whereas memantine (newer NMDA receptor antagonist) modulates the synaptic plasticity and mitigates alcohol dependence and relapse by acting on the glutaminergic system [31, 32].

Serotonergic System and Drugs Acting on it

Serotonin (5-HT) mediates cellular communication within the brain, thus playing a crucial role in brain functioning, which includes regulation of affective states, social behaviour and addiction [33], even sharing links with alcohol abuse [33]. Alcohol potentiates the function of 5-HT_3 and the somatodendritic 5-HT_{1a} receptors, Thus increasing extracellular 5-HT levels in the NAc after the alcohol administration [34]. Acute alcohol consumption potentiates 5-HT_3 receptor and these effects are antagonized by ondansetron. Similarly, chronic alcohol exposure leads to adaptive changes in 5-HT_{2A} receptors that lead to an increase in craving and decreased abstinence behaviour [35]. Psilocybin is a classic (5HT_2A agonist) hallucinogen, having clinically significant effects on alcohol and drug addiction, there is a significant decrease in the level of 5-HT_{1A} [36].

Dopaminergic System and Drugs Acting on it

Acute administration of alcohol causes activation of mesocorticolimbic system, and upon chronic administration caused an alteration in the functions of the major reward system of the brain, i.e., dopaminergic neurons of the VTA, which projects to the NAc, AMY, prefrontal cortex (PFC) and other forebrain structures [37]. In-vivo and in vitro alcohol study revealed that alcohol causes dose-dependent excitation of dopaminergic neurons in VTA and release of dopamine in NAc [38, 39]. Owing to this fact alcohol may influence the release of dopamine from the 5-HT_2 receptor, causing a flare in the firing rate of the dopaminergic neurons in the VTA and NAc, respectively, mediating indirectly alcohol-induced rewarding effects [37]. Atypical antipsychotics such as aripiprazole and olanzapine, act as antagonists to the 5-HT_2 and partial antagonists to the D2 receptor, which is hence considered suitable drugs to mitigate cue-elicited alcohol craving and a related mood disorder [40].

Neuronal Nicotine-Acetylcholine Receptors and Drugs Acting on it

Neuronal nicotine-acetylcholine Receptor (nAChR) are ligand-gated, cation-selective ion channels, consisting of an alpha (α2–α10) and beta (β2–β4) subunits [20]. Alcohol stimulates cholinergic transmissions in the meso-corticolimbic pathway, which provides an input to the dopaminergic system. During positive inference, it causes an increase in the dopamine release, which mediates the alcohol-reward behaviour [41, 42]. Several studies have substantiated that, the ethanol raises acetylcholine-induced ion flux through the alpha-4 beta-2 nicotine-acetylcholine Receptor (α4β2nAChR) [43, 44]. The alpha-3 beta-2 nicotine-acetylcholine Receptor (α3β2nAChR) meanwhile is considered as the site at which ethanol modulates dopaminergic neurons in the VTA and NAc. α4β2nAChR partial agonist and effects on 5-Chronic Serial Reaction Time performance with a focus on correct responses (attention) and premature responding impulsivity [45, 46]. Further, the study showed that varenicline reduced cue-induced relapse to alcohol, but not nicotine seeking [46].

Opioid Receptors and Drugs Acting on it

Ethanol can modify opioid transmission at different stages, and through many studies, it is known that μ, and δ opioid receptors, as well as the enkephalins and β-endorphins, play a major role in ethanol's actions in the brain [47]. The opioid system in alcohol addiction interferes with the mesolimbic dopamine transmission in the brain reward pathways. Therefore, there is an increase in the level of endorphins in the NAc [48]. Administration of the opioid antagonist causes a reduction in the release of dopamine in the NAc.

Acute alcohol administration stimulates the release of opioid peptides, particularly the β-endorphin, leading the μ - and δ -opioid receptors to activate the brain reward pathways and promote further alcohol consumption [49]. It

is demonstrated that repeated ethanol intake causes a drop in brain levels of β-endorphin and enkephalin, and at the same time up-regulates the dynorphin/κ system. Through various studies, it is noted that there is an enhanced dynorphin/κ transmission which may link to learning and memory deficits, associated with AUD and mediate cognitive control dysfunction in subjects with AUD [50]. Nalmefene μ-opioid antagonists also reduce the craving for alcohol in response to alcohol cues. It helps to reduce beta-endorphin induced impulse in the frontal corticolimbic region that promotes alcohol drinking and other risky behaviours [51]. Naltrexone is a medication primarily used in the management of alcohol dependence and opioid dependence. It modulated the β-endorphin induced dopamine release in the mesocortical region, responsible for alcohol intake and preference behaviour [52].

Cannabinoids System and Drugs Acting on it

The endocannabinoids system is responsible for behaviours related to drug-seeking and drug administration, including alcohol dependence and drinking behaviour, and modulates reinforcing and motivational effects of alcohol [53]. Acute consumption of alcohol causes an increase in the release of dopamine in NAc and inhibition of endocannabinoid transmission; further on chronic consumption becomes hyperactive. These changes produce a great impact on the development of alcohol tolerance and dependence, which further compromises with the increased synthesis of *N*-Arachidonoylethanolamine (AEA) and 2-AG in the brain and the widespread down-regulation of canobinoid receptors-1 (CB-1) and their function [53, 54]. Rimonabant, CB-1 receptors blocker, significantly reduces the dopamine-mediated alcohol-seeking behaviour [55].

Miscellaneous

Apart from neurotransmitters, some neuropeptides, hormones and enzymes can be a potential target for the management of AUD.

Oxytocin

The activity of dopaminergic neurons in mesolimbic pathways determine the reward value of both natural and substance-related reinforces such as consumption of high caloric foods and drugs of abuse such as ethanol [56]. The action is accomplished by facilitating a ventral-to-dorsal shift to activation in corticostriatal loops. The neuropeptide oxytocin impacts upon the neurons in the mesolimbic pathway, thereby providing the possibility of oxytocin regulation of these behaviours [56].

Neurokinin-1 (NK-1)

NK-1 receptor works on hypothalamic, pituitary, adrenal (HPA) axis through G-protein-coupled corticotrophin-releasing factor receptor and nigrostriatal dopaminergic pathway, through which it potentiates synaptic changes in a different brain region involved in alcohol preference behaviour [57, 58]. NK-1 receptor regulate oxytocin secretion [59]. Further, NK-1 Receptor antagonist and oxytocin attenuates emotional challenges and anxiety-like symptoms in AUD [59]. LY686017 is a neurokinin antagonist, which obstructs the neurokinin mediated substance P and progesterone release by inhibiting the anterior pituitary hormonal modulation in reward and anti-reward system [60].

Phosphodiesterase Enzyme

Cyclic adenosine monophosphate (cAMP) signalling cascade has been implicated in mediating behavioural responses to alcohol phosphodiesterase, an enzyme that specifically catalyzes the hydrolysis of cAMP in the mesolimbic reward system and induces positive reinforcement. Ibudilast, a non-selective phosphodiesterase inhibitor, reduces alcohol drinking and relapse in alcohol-preferring rats [61].

Glucocorticoid

The main neuroendocrine stress system and consequent alterations in brain glucocorticoid receptor expression accompany compulsive-like alcohol intake in rats. The glucocorticoid receptor antagonist mifepristone reduces alcohol intake in alcohol-dependent rats but not in nondependent animals [62].

Ongoing Research for Novel Neurochemical Target and Biochemical Marker for AUD

Neurochemical and Biochemical Marker

Orexin/Hypocretin

Preclinical and clinical study suggested that, the orexinergic neurons are widely projected throughout the brain and especially in VTA and NAc and potentially involved in the development of AUC [63]. Activation of the orexinergic system contributes to the motivation of alcohol-seeking behaviour. Orexinergic system stimulates brain reward centre during the earlier stage of alcohol drinking and increases impulsivity [64]. Further, pharmacological modulation of

the orexinergic system ameliorated the alcohol reward as well as abstinence which further confirms the involvement of orexinergic system in alcoholism [63]. Recently, an open pilot trial demonstrated that non-selective blockage of orexin receptor (OXR1 and OXR2) with suvorexant is efficacious for a patient with insomnia and alcoholism [65].

Ghrelin

Ghrelin hormone is involved in the regulation of food intake and energy balance. Growing evidence suggested that ghrelin modulates mesolimbic reward pathways and therefore, is directly involved in the pathophysiology of substance use disorders such as alcohol dependence. Recently Geisel et al., demonstrated that the long term effect of baclofen for the treatment of alcohol dependence could be easily accessed by measuring total plasma level of acylated ghrelin level [66]. Statistical analysis revealed that total plasma ghrelin level significantly decreased in the group of abstinent patients receiving high-dose (30–270 mg/d) of baclofen. Moreover, the plasma acylated ghrelin level increased in the group of relapsed patients under baclofen treatment. Together, these findings substantiated that the long-term response to baclofen treatment in AUD can be monitored by assessing total and acylated ghrelin plasma levels [66].

Biochemical Markers

Biochemical markers for substance and drug abuse such as alcohol dependence helps the clinician to ascertain the alcoholism or AUD. Earlier marker relied on the effect of alcohol on blood cells like *mean corpuscular volume* (*MCV*) or on body organs such as liver *aspartate transaminase (AST) and alanine transaminase (ALT)*. However, these markers have lower specificity towards alcoholism as it could also get altered in other diseases. Further, it is hard to record baseline level with older biomarkers as it raises only after prolonged use of alcohol. Therefore, the propensity of the detection of acute alcohol intake is less. Hence, the detection of recent and acute intake of alcohol was a challenge. This has also simultaneously led to the quest for newer biomarkers that can detect recent alcohol use. The biomarkers such as *5-Hydroxytrptophol (5-HTOL),* urinary *Ethyl Glucuronide (EtG)* and serum *Fatty Acid Ethyl Esters (FAEE)* are direct products of ethanol and are relatively unaffected by disease conditions [67]. They are detected soon after moderate-heavy bout of alcohol use and are present in the body fluids for a shorter period of time. However, detection of biomarkers is costly, and hence, combining different biomarkers together offers the best solution to detect alcohol use [66].

Medications Involved in the Treatment of AUD

The approved drugs with pharmacotherapy, mechanism of action (MOA), clinical report and adverse effects are enlisted detail in Table 1.

Drugs Under Phase-II Trial

Ghrelin Receptor Inverse Agonist PF-5190457

Clinical study demonstrated that, when PF-5190457 is co-administered (100 mg twice in a day) with alcohol. PF-5190457 reduced alcohol craving during the cue-reactivity procedure [68]. This finding provides the first translational evidence of safety and tolerability of the PF-5190457 when co-administered with alcohol. The mechanism involved is the facilitation of GABAergic system which reduces the plasticity of alcohol reward [69]. Further, the pharmacokinetics, pharmacodynamics and behavioural data supported the continued research of PF-5190457 as a potential pharmacological agent to treat AUD [69].

NK-1 Antagonist LY686017

NK-1R antagonist mitigated the conditional place preference by reducing extracellular dopamine content in the NAc [70]. LY686017 obstructs the neurokinin mediated substance P and progesterone release by inhibiting the anterior pituitary hormonal modulation in reward and anti-reward system [60]. GlaxoSmithKline has a dual NK1R/NK3R antagonist, GSK1144814, in the pipeline for future clinical trials for psychiatric patients suffering from AUD [71].

Nociceptin (NOP) Receptor Antagonist BTRX-246040

BTRX-246040 reduced depression symptoms in a second trial with heavy alcohol drinkers. Clinical study demonstrated the efficacy of BTRX-246040 in major depressive disorder (MDD) patients. In this study, administration of BTRX-246040 (40 mg, p.o.) reduced alcohol drinking behaviour in depressed patients. In addition, plasma levels of gamma-glutamyl transferase were decreased by BTRX-246040 compared to placebo control thus implying an improvement in liver function. Collectively, the clinical data reviewed within this review suggest that BTRX-264040 normalize the dysfunction in reward circuits [72].

Table 1 Medications involved in the treatment of AUD

Drugs and doses	Approved pharmacotherapy	Mechanism of action	Clinical report	Adverse effects
Naltrexone (50 mg single dose daily)	Opioid antagonist reduced alcohol craving	Naltrexone is an opioid antagonist and primarily used in the management of AUD and opioid dependence. Naltrexone works through dopaminergic pathway in mesolimbic system and reduces firing of dopamine in NAc and reduces alcohol intake and preference behaviour [79]	In a randomized controlled trial, it was found that daily single dose of naltrexone intake attenuated drinking behaviour and also mitigated relapsing behaviour among heavy drinkers [79]	During early treatment abdominal pain, nausea, vomiting [80]
Acamprosate (333 mg tabletsTwo tablets three times daily)	Maintenance therapy for alcohol abstinence	Acamprosate is a NMDA receptor antagonist with modest $GABA_A$ receptor agonistic activity [81]. Acamprosate may modulate NMDA receptors via regulatory polyamine sites. All these mechanisms may be used for the treatment of alcohol dependence and relapse [82]	The double-blind, randomized multicentric trial was carried out. Abstinence figures followed a different dose of placebo [80]	Constipation, Weight gain/loss, fatigue, muscle/joint pain, decrease in sexual desire [83]
Disulfiram (250–500 mg/d orally)	Disulfiram therapy is aversive therapy which works in abstinent subjects who really want to quit the habit of drinking	Disulfiram inhibits the aldehyde dehydrogenase thereby it inhibits the metabolism of acetaldehyde to acid. Therefore, the accumulation of acetaldehyde causes the disulfiram–ethanol reaction which results in increased pulse and respiration, tachycardia, facial flushing, nausea, vomiting [84]	In randomized controlled trial, patients treated with disulfiram have some effect on short-term abstinence relapse in some drinking days when compared with placebo [85]	Drowsiness, tiredness, headache, acne, and Hepatotoxicity

Drugs and doses	Adjuvant therapy or repurposing therapy	Mechanism of action	Preclinical and clinical report	Adverse effects
Non-FDA approved or off-line drugs				
Nalmefene (18 mg/d as needed)	Alcohol dependence and Opioid dependence.	Opioid μ receptor antagonist, and partial agonist to k receptor [86], and may act on frontal cortical-limbic circuits to reduce impulsivity that promotes alcohol drinking and other risky behaviours [51].	The randomized double-blind study revealed nalmefene reduced alcohol consumption and enhancing the sedative properties of alcohol [87].	Fast heart rate, stomach pain, muscle/joint pain, dizziness, headache, hypotension [80].
Varenicline	Reduced alcohol-seeking behaviour and smoking cessation.	A partial agonist to ά4β2nAChRs for alcohol dependence and partial agonist to the nicotinic receptor for smoking cessation [88], which acts through the mesolimbic dopaminergic system and reduces the reward and preference toward alcohol use [89].	Clinically validated ά4β2nAChRs partial agonist and act by reducing the ability of alcohol to activate dopamine release in the NAc [90].	Nausea, constipation, abnormal (vivid, unusual, or strange) dreams, flatulence, and vomiting [91].

Table 1 (continued)

Drugs and doses	Adjuvant therapy or repurposing therapy	Mechanism of action	Preclinical and clinical report	Adverse effects
Topiramate (75–300 mg/d in two divided doses)	Anticonvulsant Reduced alcohol dependence and seeking behaviour.	It acts by inhibiting mesocorticolimbic dopamine release via facilitation of GABA activity, antagonizing glutamate AMPA, and kainate receptors and antagonizes alcohol's rewarding effects [92, 93].	In randomized, double-blind, placebo-controlled trials with more than 600 patients, compared to placebo, topiramate reduced the number of heavy drinking days and increased days of abstinence by reducing the craving for alcohol [92].	Tiredness, loss of coordination, tingling of the hands/feet. Cognitive deficits [80].
Gabapentin (600–1800 mg/d in three divided doses)	Anticonvulsant Reduces alcohol consumption and craving	Facilitation of GABA mediated chloride channel opening and enhances GABA release. Modulate voltage-sensitive calcium channels [94]. Alcohol drinking suppressed by stimulating a $GABA_B$ receptor in the NAc, Ventral Pallidum. Also reduces beta-endorphin linked alcohol preference pathway [15]	In a randomized, double-blind, placebo-controlled trial with alcohol-dependent subjects, after 28 days of treatment. Gabapentin reduced the number of heavy drinking days and increased days of abstinence compared to the placebo group [95]	Drowsiness, dizziness, loss of coordination, tiredness, sedation and respiratory failure [96]
Zonisamide (100 mg/day)	Newer anticonvulsant improvement in alcohol craving and alcohol consumption	It acts on the glutaminergic system and reduces synaptic plasticity that leads to a decrease in alcohol dependence. Also acts via inhibition of 'T' type calcium current. It also alters the concentration of γ-glutamyl-transferase which is a measure of alcohol consumption [97]	Open-label study as per DSM-IV demonstrated that, zonisamide treatment cause significant improvement in the visual analogue scale for craving severity scores and weekly drink consumption in 22 outpatients [98]	Muscles fatigue, somnolence, dizziness and ataxia [98]
Pregabalin (Maximum 450 mg/day)	Newer congener of gabapentin	Pregabalin is selectively binds to the α2 subunit of voltage-gated calcium channels and inhibits the release of excitatory neurotransmitters [99]	In the open-label trial, treatment with pregbalin caused a significant progressive reduction of both craving and withdrawal symptomatology in 20 patients compared to placebo [100]	Rashes, allergic reactions
Baclofen (30–180 mg/day)	Centrally acting muscle relaxant, reduces the acquisition of alcohol-drinking behaviour	A selective $GABA_B$ receptor agonist, voltage-gated N-type calcium channel blocker and also acts as a suppressor of alcohol-stimulated dopamine release in the mesolimbic dopamine system probable mechanism in the treatment of AUD [101]	In preclinical studies treatment with baclofen showed dose-dependent reduction in the self-administered alcohol in rats under operant self-administration conditions [102]	Drowsiness, weakness, dizziness, tiredness, trouble sleeping, headache nausea, constipation, increased urination [102]
Ondansetron (4 µg twice daily)	The antiemetic drug, beneficial for AUD	5-HT3 receptor antagonist [103]. Ondansetron act through the amygdala to antagonize the aversive behaviour caused by alcohol withdrawal [104]	An oral (4 µg/kg dose solution) administration of ondansetron twice in a day reduces alcohol withdrwal symtoms compared to placebocontrol trial [105]	A headache, dizziness, lightheadedness, drowsiness, tiredness, or constipation

Table 1 (continued)

Drugs and doses	Adjuvant therapy or repurposing therapy	Mechanism of action	Preclinical and clinical report	Adverse effects
Ivermectin	Anti-parasitic agent, and reduce alcohol intake	The allosteric modulator of P2X4R receptor novel target for AUD treatment [106]	Randomised double-blind, shown a prescribed dose of ivermectinreduces the number or severity of adverse effects during alcohol administration or throughout the treatment schedule [107]	Swelling of joints, tendons and in lymph node, itching or skin rash [107]
Ibudilast (10 mg delayed-release capsules, target dose 50 mg)	Neuroimmune modulator, reduce alcohol drinking and relapse	A non-selective phosphodiesterase inhibitor. Ibudilast inhibits the catalytic hydrolysis of cAMP. The catalytic hydrolysis of cAMP in the mesolimbic reward system is responsible for positive reinforcement [108]	Ibudilast shows a substantial reduction of alcohol consumption in rodent model alcohol consumption. Ibudilast prevents catlytic hydrilysis of cAMP reduces alcohol drinking and relapse behaviour [61]	Anorexia, nausea, vomiting abdominal pain, dyspepsia, dizziness, headache
Mifepristone (600 mg daily)	Anti-progestin	The increased expression of glucocoriticiod receptor has been observed in AUD. The mechanism involves is the activation of HPA axis- induced activation of reward pathway. The glucocorticoid receptor antagonist mifepristone reduces alcohol seeking behaviour and imulsivity [109, 110]	Reduce alcohol craving and drinking in nontreatment-seeking outpatient alcoholics relative to placebo. The probable reason behind this result is normalization of the HPA axis brain extra hypothalamic stress systems [111]	Nausea, vomiting, diarrhoea, weakness, or dizziness
Oxytocin (intranasal oxytocin (40 IU with a 20 IU booster)	Uterine stimulant	Modulation of dopamine receptor is a probable resion for oxytocin receptor to impair ethanol drinking behaviour [56, 112]. The action is accomplished by facilitating a ventral to dorsal shift [113]	Oxytocin receptor (OxtR) pharmacological modulation was able to modulate the different processes of ethanol-induced conditional place preference including acquisition and reinstatement [114]	Sinus pain or irritation
Memantine (dose of 40 mg/d)	Cognition enhancer, Reduced Alcohol drinking behavior, prevents alcohol dependence	New NMDA receptor antagonist related to acting on NMDA induced synaptic plasticity, altered by regular alcohol intake [32]	Memantine is effective against acute reward and withdrawal effect but inefficient as a relapse-preventing drug in a pre-clinical model of alcohol dependence [115]	Headache, blurred, chest pain, numbness, seizure
Prazosin (daily dose 16mg)	Adrenergic blocker reduces alcohol drinking behaviour	Selective α1 antagonist [116]	Prazosin shows a decrease in alcohol intake during prolonged treatment and may be useful in the treatment of AUDs. Prazosin may also be useful for preventing the initiation of drinking in individuals with a family history of AUD [117]	A headache, drowsiness, blurred vision, tiredness, weakness, nausea, vomiting, diarrhoea, or constipation

Table 1 (continued)

Drugs and doses	Adjuvant therapy or repurposing therapy	Mechanism of action	Preclinical and clinical report	Adverse effects
Psilocybin (25-40 mg/70 kg orally)	Hallucinogen mood stabilizer Reduced regular intake of alcohol	5HT2A agonist, act as the supplement of alcohol stabilizes the mood and behaviour [118]	Participants exhibited significant improvement in drinking, with large pre-post effect sizes, as well as substantial changes in psychological measures relevant to drinking. Much of the improvement occurred after the administration of psilocybin, at the time participants had received four weeks of psychosocial treatment and 4–6 h of assessment [36]	Convulsions
Rimonabant (20 mg/day)	Rimonabant is a anti-obesity, anorectic also reduces alcohol reinstatement in alcohol dependence	The CB1 blocker rimonabant was found to decrease alcohol consumption, possibly by indirect modulation of dopaminergic neurotransmission [55, 119]	Double-blind, placebo-controlled, suggested that, the CB1 blocker rimonabant (20 mg/d) significantly reduces the alcohol relapsing behaviour alcohol-dependent patients [120]	Depressive disorders or mood alterations. Nausea and upper respiratory tract infections
Aripiprazole (5–15 mg/day)	Anti-psychotic, Anti-depressant. Prevent reward and alcohol intake to drinking behaviour	Partial D2 antagonist. Partial agonist of the serotonin 5-HT_{1A} receptor [121]	Clinical study revealed that, the sub-chronic administration of aripirazole reduces activation of brain reward centre. Moreover, it also inhibits the over activity of dopaminergic activity in NAc [122]	Insomnia, nervousness, tiredness, excess
Levetiracetam (Tablets with 500 mg)	Anti-epileptic, Anti-anxiety, Anti Alzheimers Reduced Alcohol dependence	It acts via modulation of synaptic neurotransmitter release by binding to the synaptic vesicle protein SV2A in the brain and inhibition of presynaptic calcium channels which reduces neurotransmitter release and acts as a neuromodulator, reducing synaptic plasticity due to chronic intake of alcohol [106]	Double-blind, randomized crossover trial shown that Levetiracetam attenuates alcohol consumption in an open-label study of treatment-seeking, alcohol-dependent subjects [123]	Somnolence, decreased energy, headache, dizziness
Quetiapine (25 to 200 mg nightly)	Atypical antipsychotics prevent alcohol dependence and relapse	Specifically, the D1 and D2 dopamine. It also acted through a serotonergic pathway of alcohol dependence [124]	In an open-label clinical study, shown that quetiapine decreased alcohol consumption, craving for alcohol, maintaining a reasonable level of tolerance [125]	Seizures,high blood sugar, prolonged erection, and neuroleptic malignant syndrome

Table 1 (continued)

Drugs and doses	Adjuvant therapy or repurposing therapy	Mechanism of action	Preclinical and clinical report	Adverse effects
Minocycline (200 mg/day)	Stimulant-induced Alcohol addiction	Minocycline attenuated amphetamine-induced acute dopamine release and subsequent behavioural sensitization through GLuR-1 receptor and interacts with brain glutamate (GluR-1) and D2 neurotransmission [126]	In preclinical studies, minocycline attenuated amphetamine-induced acute dopamine release and subsequent behavioural sensitization. Clinical study: subjects were randomly assigned to acute, double-blind challenge with both dependence and preference, the study revealed that minocycline reduced stimulant-induced alcohol dependence but had not affected the preference behaviour [127]	Dizziness, loss of balance, lightheadedness, and tinnitus
Mecamylamine (10 mg per day)	Reduced ethanol-induced reinforcement	Mecamylamine acts on the nicotinic receptor and reduces nicotine-induced sensitization of dopaminergic pathway and also reduced nicotine-dependent alcohol dependence [128]	The rat and the associated accumbal dopamine overflow is blocked by ventral tegmental mecamylamine [129]	Parasympathetic-blocking activity, urinary retention,and loss of visual accommodation in some patients [130]
Olanzapine (2.5–5 mg/day)	Alcohol dependence and preference	Dopamine-D2/D4, Adenosine A2, and 5HT-2 receptor antagonist [131]. The effect of olanzapine (a D2/D4 antagonist) is more pronounced among individuals, and 5HT receptor antagonist property plays a role in reduced drinking behaviour as mentioned [132]	Double-blind, randomized, parallel-group clinical trial represent that olanzapine reduced alcohol craving and preference behaviour in the adult [132]	Sexual dysfunction gynecomastia, menorrhagia, amenorrhea, and galactorrhea
Doxazosin (16 mg/day)	Reduces alcohol Drinking and seeking behaviour	Doxazosin α1-adrenergic antagonist, in decreasing alcohol drinking in rat models of alcohol dependence without affecting locomotor activity [116, 133]	Clinically reported that Doxazosin significantly reduced alcohol intake, increased water drinking [133]	A substantial increase in maximum urinary flow rate
Mirtazapine (15–30 mg/day)	Alcohol detoxification	Mirtazapine, a noradrenergic and specific serotonergic antidepressant. Mirtazapine used adjunctively to short-term psychotherapy, may help the detoxification process by minimizing physical and subjective discomfort [134, 135]	The clinical application demonstrated that mirtazapine attenuated the alcohol detoxification in healthy volunteer [136]	Chronic use of mirtazapine causes tastes aversion test and by causing lower lip retraction [134, 135]
Novel agents under trial for AUD				
PF-05190457 (100 mg twice in a day)	National Institute on Alcohol Abuse and Alcoholism (NIAAA) suggested PF-05190457 for alcohol craving (phase-2) trial	Ghrelin inhibitor	Double-blind, randomised control trial with 55 patients suggested that sub-acute use of PF-05190457 mitigated the alcohol craving through inhibition of ghrelin hormone release. Clinical phase-II trial study suggested that, PF-5190457 (100 mg twice in a day) reduced alcohol craving during the cue-reactivity in AUD [68]	Long term use of PF-05190457 may reduce motivation for normal food intake [68]

Table 1 (continued)

Drugs and doses	Adjuvant therapy or repurposing therapy	Mechanism of action	Preclinical and clinical report	Adverse effects
LY686017 (50 mg daily orally)	Stressed induced Alcohol dependence	NK1 receptor regulate oxytocin secretion [137]. LY686017 is an NK1 Receptor antagonist that attenuates emotional challenges and anxiety-like symptoms in AUD [59]	The controlled randomized clinical study reported that LY686017 reduces alcohol impulsivity and improved overall well-being with concomitant cortisol responses [60]	Long-term treatment LY686017 may cause anxiety and depression [57]
BTRX-246040 (40 mg daily orally)	BTRX-246040 is a nociceptin (NOP) Receptor Antagonists which reduced depression symptoms in a second trial with heavy alcohol drinkers	NOP Receptor Antagonists significantly reduced negative bias as assessed by the facial recognition test within 1 week of treatment and decreased depression symptoms after 8 weeks	Randomized, Double-Blind, Placebo-Controlled study on BTRX-246040 (40 mg, p.o.) demonstrated that, daily single dose administered of BTRX-246040 reduces being for alcohol drinking in a patients with Major Depressive Disorder and AUD	BTRX-246040 can reduces sensitivity and some time loss sensation [72]
SB 334867 (20 mg/kg)	SB 334867 reduces alcohol-seeking behaviour and motivation for self-administration	Non-selective OXR1 and OXR2 antagonist for the treatment of alcohol-seeking behaviour and motivation for self-administration	A preclinical study on ethanol self-administration has been reduced by SB 334867	Narcolepsy [138]
Combined medicine under Phase-II trial				
ALKS 3831 Combination of (Samidorphan + olanzapine)	Mixed type mechanism of action	Useful for the treatment of Schizophrenia and AUD	A Phase-II, Randomized, Double-blind Study to Evaluate Efficacy, Safety, and Tolerability of ALKS 3831 in Subjects with Schizophrenia with Alcohol Use Disorder	Long term therapy may cause extra pyramidal side effect [139]
Ondansetron + cognitive behavioural Placebo + cognitive behavioural therapy Ondansetron + topiramate + cognitive behavioural therapy	Mixed type mechanism of action	Treatment with combination reduces excitatory neurotransmitter and facilitates inhibitory neurotransmitter in AUD	A Phase-II, Randomized, Double-blind Study revealed better improvement in the behavioral symptoms.	Treatment with combination may produce depression in long term therapy.

Non-selective OXR1 and OXR2 Antagonist SB 334867

SB 334867 significantly reduced compulsive-like consumption at doses lower than those reported to reduce quinine-free alcohol intake. The dose of 3-mg/kg SB 334867, in particular, suppressed only compulsive-like drinking [73]. Furthermore, SB 334867 did not alter saccharin and quinine consumption. In addition, the OX2R antagonist TCS-OX2-29 (3 or 10 mg/kg) did not alter intake of alcohol with or without quinine. Together, these results suggest that OX1R signalling is particularly important for promoting compulsive-like alcohol drinking and that OX1Rs antagonist might represent a novel therapy to counteract compulsive aspects of human AUD [74].

Discussion and Conclusion

Targeting the neurochemical system is an important strategy for the treatment of AUD. As per the present evidences, the alcohol interacts with various inhibitory and excitatory neurotransmitters. The drugs presently used are effective for the alcoholism but for a shorter period of time. Targeting of opioid, glutaminergic and serotonergic system depletes dopamine in NAc and reduces alcohol preference tendency in clinical patients. However, cannabinoid drugs and GABA mimetic are most effective for reward circuitry in NAc. As per preclinical and clinical study reports, the targeting of adenosine receptor would be a more effective treatment strategy because it forms a communication between both excitatory and inhibitory neurotransmitters. Recent preclinical and clinical evidence also suggested that, targeting of orexin and ghrelin would also be a novel approach as it directly controls food reward and energy homeostasis. Apart from that, the present review also addressed the recently used or under trial biomarker for AUD.

Half a century has passed since the discovery of AUD as a disease, but still, we have only managed to discover a few drugs, with some of them proving to be controversial in the later run. So, as the situation demands, there is an immediate need to find a proper mechanism to treat AUD, as the exact mechanism by which ethanol exerts its effects on the brain is still unknown. Significant complexity occurs because alcohol is, directly and indirectly, linked with the function of almost every neurotransmitter. It is very well known that neurochemical approach favours the pharmacotherapy of AUD as the alcohol interacts with specific neuronal membrane proteins, thus involved in the signal transmission, which results in a change in neuronal activity [75]. Alcohol interacts with two membranes receptor: $GABA_A$ and NMDA ion channel receptors, which indeed causes the enhancement of the inhibitory effect of $GABA_A$ and antagonizes the excitatory effect of glutamate. In the case of the brain reward system, the dopaminergic, serotonergic and opioid system is also well affected by the drugs [2]. As mentioned in the review, noradrenergic, neuronal nicotine acetylcholine receptors and cannabinoid systems also plays a significant role in the neurobiology of alcohol interactions.

The curiosity of research scientists, with their organized study, will gather the needs for the pharmacological treatment for AUD. The heterogeneity of AUD patients and the complex aetiology of the disease and even different patterns of consumption, onset of drinking and drinking behaviour have involved in the pharmacotherapy [2]. For example, acamprosate shows greater efficiency in promoting naltrexone efficacy, and even showed a more significant effect in a patients who had already undergone detoxification [76]. Naltrexone is more efficacious in reducing heavy drinking and showed more considerable medication effects than acamprosate for the treatment of AUD yield mixed finding. Other medications like nalmefene, gabapentin, varenicline, topiramate, and zonisamide showed good efficacy, with side effects that were mild to moderate in intensity. However, baclofen, ondansetron had a mixed preliminary results but is awaiting for finding of additional studies. A final group (levetiracetam, quetiapine, aripiprazole, and SSRIs) had promising preliminary results but has not demonstrated efficacy in larger trials [77]. Through various studies, we concluded that rather than single-agent treatment, there should be a multi-drug treatment; for example, disulfiram may cause potentially fatal hepatotoxicity. Taking into consideration the alcohol drinking is frequently related to liver disease [78]. Thus it would be more beneficial to go for combination therapy including disulfiram and other agents such as acamprosate or naltrexone [20]. Thus, further studies in the following area are vital to arrive at meaningful answers, which will help to optimize pharmacotherapy for AUD.

In conclusion, the development of AUD mainly involves the modulation of biomarkers which are regulated by neurotransmitter or other neurochemical systems. The FDA approved drugs target limited neurochemical systems and mainly opioid and glutaminergic systems. However, these systems are also modulated by various other neurotransmitters like dopamine, seorotonin, GABA, adenosine, acetylcholine and adrenaline. In recent, an ongoing preclinical and clinical study suggested that, newer neurochemical marker such as orexin, ghrelin, neurokinin and nociceptin could also alter dopaminergic, serotonergic, cholinergic and noradrenergic systems. Therefore, targeting these markers would be a better treatment approach for AUC due to established role in the modulation of major neurochemical contributing in the development of AUD. These findings are under phase-II trial and based on their overall efficacy and safety it can be used as a newer treatment strategy for AUD.

Future Perspective and Social Relevance

The development of the neurochemical and combination based therapy which targets multiple neurotransmitters involved in the positive reinforcement and development of withdrawal symptoms is essential to treat group of symptoms of AUD. In our society, AUD mostly leads to cognitive impairment so that inclusion of cognitive or motivational therapy can further improve the quality of life of the patients affected by AUD. Moreover, testing of biochemical and neurochemical markers can increase the understanding of heritable factors involved in AUD. In future, these may serve as a guidance to clinicians in identifying and prescribing the most suitable pharmaceutical interventions to AUD patients.

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Compliance with Ethical Standards

Conflict of interest The authors have no conflict of interest.

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