MMSL
Military Medical Science Letters
Since 1925

Mil. Med. Sci. Lett. (Voj. Zdrav. Listy) 2024, 93(1), 140-149
ISSN 2571-113X (Online)
DOI: 10.31482/mmsl.2023.002

## REVIEW ARTICLE

# GLUTAMATE AS A TARGET THERAPY FOR ALCOHOL DEPENDENCE DISORDER

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Received 8th September 2022.
Accepted 5th January 2023.
Published 1st March 2024.

**Summary**

Alcoholism (Alcohol dependence) is considered a serial health problem because of tendency for consumption more alcohol, control losing and the physical dependence development. This cycle in most often featured by periods of craving, abstinence, and relapse. The cholinergic, adrenergic, dopaminergic, glutamatergic, GABAergic, serotonergic, peptidergic, and different neurotransmitter systems in the brain are affected by alcohol consumption. The development of alcohol dependence is attributed to neuro-adaptations within the extended amygdala and mesocorticolimbic systems. Principally, the glutamatergic neurotransmission variations that resulted by alcohol consumption, lead to researches recommended in a focus on normalization of glutamatergic neurotransmission and glutamatergic receptors as a targeting therapy. Glutamatergic receptors are classified to ionotropic glutamate receptors (AMPA, Kainate, and NMDA) and metabotropic receptors. Sodium dependent excitatory amino acid transporters (EAATs) and vesicular glutamate transporters (VGLUTs). Additionally, cysteine-glutamate antiporter which regulates cysteine -glutamate exchange at the synapse. At least 90% of extracellular glutamate displace particularly by GLT1. Ceftriaxone, GPI-1046 and MS-153, upregulate expression of glutamate transporter 1 (GLT1) in mesocorticolimbic brain region.

*Key words: Alcohol dependence; Glutamate; GLT1; Pharmacotherapy*

## 1. Introduction

The third common cause of avoidable death in the world and still global socially major trouble that affecting more than 18 million people and mortality rate in U.S. about higher than 100,000 deaths are caused by alcoholism or alcohol use disorders (AUDs) (1, 2). Economically, The cost society of AUDs each year about 200 billion dollars (3). The important features for diagnosing of AUDs and for advancing treatment strategies are depended on the extent of alcohol consumption and volume consumed per unit time (4, 5). The pharmacological efficacy for treatment of AUDs is altered by genotypic and/or phenotypic characteristics associated with drinking typologies and development of AUD by enhancing excessive early alcohol drink was observed through many of the gene variants (6, 7).

Alcohol dependence is a disorder characterized by four symptoms including loss of control, craving, physical dependence and tolerance development according to Alcohol Abuse and Alcoholism definition by the National

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Institute (8). In the early stages of this disease is progressed from euphoric, rewarding and positive-reinforcement aspects (e.g., autonomic and motor activation and facilitating pro-social behavior) to the dysphoric and negative-reinforcement associated (e.g., withdrawal syndrome) in the later stages of chronic alcohol use. These changes from positive to negative reinforcement is correlated with brain reward systems downregulation and the brain stress systems upregulation, which across addiction cycle then succeed by neuroplastic variations in central reward neurocircuitry (as in extended amygdala and mesocorticolimbic system) (9).

Homeostasis exists between excitatory and inhibitory neurotransmission in the normal functioning brain. This equilibrium is disturbed by acute alcohol consumption through attenuates excitatory and enhances inhibitory neurotransmission. Glu and GABA consider are a targets key of alcohol through increases inhibitory neurotransmission via GABA and decrease excitatory neurotransmission via Glu simultaneously (10, 11). Following, chronic alcohol abusing, the brain repays the depressant effects of alcohol to maintain inhibitory (e.g., GABA) and excitatory (e.g., glutamate) neurotransmission homeostasis through enhancing excitatory activity and decreasing inhibitory activity (12, 13).

**2. Glutamatergic neurotransmission in mesocorticolimbic system.**

Accompanied with addiction, the primary glutamatergic projections, including (the extended amygdala and the mesocorticolimbic dopamine system and in addition to learning and memory brain mediating regions). The primary neurocircuit is the mesocorticolimbic system which is a mediating reward and reinforcement salience that is mostly, but not constantly, linked with a positive valence (14), as showed in (Figure 1) (15). It was demonstrating that activation of the glutamatergic projections from the amygdala results in anxiogenic and aversive behaviors, while activation of the GABAergic parallel projections results in anxiolytic and appetitive behaviors, as-regards to the rewarding/reinforcing dual valence-processing stimuli within the extended amygdala and mesocorticolimbic system (16). So, from these neurocircuits, the early stages of abuse of ethanol during the experimentation given positive reinforcing and rewarding action, due to the acute inhibition effects of ethanol consumption on glutamatergic activity and stimulate GABAergic activity. The positive reinforcement during early stages of alcohol abusing drives the individual for continuing usage, by consumes or self-administers more alcohol to give the pleasant and euphoric effects. By the mesocorticolimbic dopamine system, controlling the positive reinforcement is mediated greatly by glutamatergic activity for the most part. Comparatively, the chronic effects of ethanol cause inhibition of GABAergic activity and potentiate glutamatergic activity, and observed consequence of elevate in dopaminergic activity in prefrontal cortex (PFC), it results in an aversive condition particularly under withdrawal stats. It also recruits increasing corticotrophin releasing factor anxiogenic activity and glutamatergic neurotransmission in extended- amygdala. Collaborative with these latter effects evoke continue using of alcohol and drugs in a try to reverse or delay the onset of withdrawal -associated symptoms. At least in part, the extended amygdala mediates these withdrawal symptoms related to irritability and anxiety with accompanying autonomic and heightened physiological responses. These responses are mediated not only by increased glutamatergic activity but also potentiate corticotrophin releasing factor (CRF) is anxiogenic peptidergic activity as against to anxiolytic neuropeptide Y (NPY) activity in extended amygdala, in particular the amygdala and bed nucleus of stria terminalis (BNST) (17). In final stages of alcohol dependence, the neuroplastic variations of the extended amygdala become more pronounced while the neuroplastic variations in the mesocorticolimbic system are retained (18), as in (Figure 1) (15).

**2.1 Interactions of glutamatergic neurotransmission with alcohol**

Glutamate is a main central excitatory neurotransmitter, which acts on two expansive classes of receptors are ionotropic and metabotropic. The ionotropic receptors are ligand-gated ion channels receptors and are subdivided into alpha-amino-3-hydroxy-5-methylisoxazole-4-propionic acid (AMPA), N-Methyl-D-aspartate (NMDA), and Kainate receptors by depend on sensitivity to their corresponding agonists, they are responsible for fast excitatory transmission (19). The metabotropic receptors (mGluR) are G-protein coupled receptors and classified into eight mGluR subtypes and three groups which are Group I (mGlur1& mGluR5), Group II (mGluR2 & mGluR3) and Group III (mGluR4,6,7,8). These types of receptors are responsible for slower long-lasting effects in the postsynaptic cells (20).

The exposure to ethanol alcohol consumption will alter the activities of central glutamatergic system and these alterations differ according to the intensity of ethanol abusing. The effect of acute alcohol exposure in central

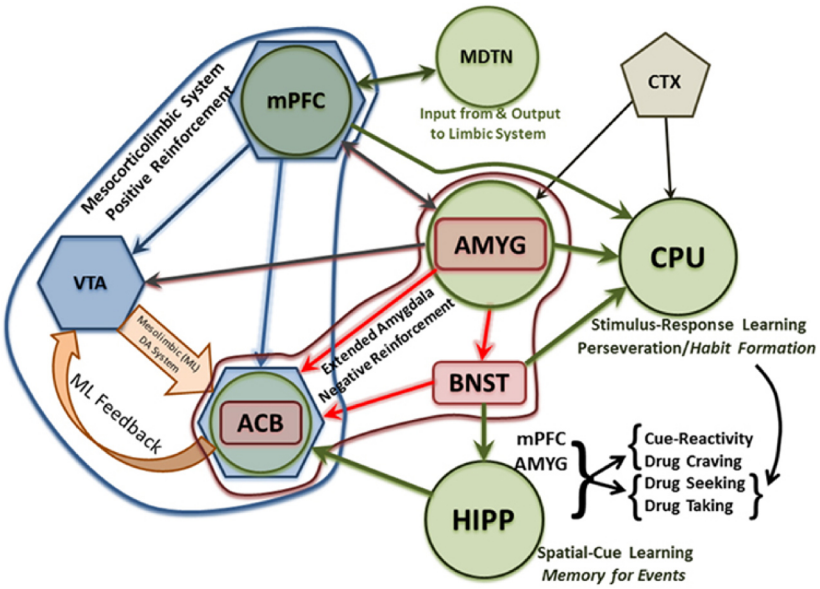


**Figure 1.** Diagram of glutamatergic neurocircuits in mesocorticolimbic system (15).

reward brain regions(amygdale) shows to drop in extracellular glutamate levels and reduce glutamatergic transmissions (21). While at chronic ethanol exposure, shows to increase in extracellular glutamate levels in mesocorticolimbic brain regions. Additionally, the consumption effects of alcohol on NMDA, mGluRs and expression a glutamatergic receptor scaffolding protein (Homer) subunit in the extended amygdala are also altered by the period of withdrawal alcohol (22).

Intracellularly, the ethanol will non-competitively inhibit the NMDAR-mediated influx of calcium to these brain regions including {the cortex, amygdala, ventral tegmental area (VTA) and hippocampus} (23). Moreover, the physiological and psychoactive effects of ethanol are because of several receptor systems activation. Including: N-Methyl-D-aspartate (NMDA), the action of ethanol consumption on activity of NMDA receptor are occurred by internalization and phosphorylation of receptor subunits which permit $Ca2^{+}$ influx inside the cell, in turn promote long-term potentiation (LTP) induction, a key element of memory and learning, causing by example; to habit formation (24). Many studies have been shown that withdrawal effects of alcohol in brain regions is associated with elevation in transmission of excitatory amino acid and dopamine signaling alterations, resulting in executive functions deficits. And together, these impact the quality of life and promote the relapse probability causing events of different syndromes like seizures, which could be inhibited by using NMDA receptor blocker (25).

## 3. Role of glutamate transporters in glutamate homeostasis

Extracellularly, glutamate (excitatory neurotransmitter) uptake is regulated by a family membrane-bound protein pump which are glutamate transporters, these transporters are exist on both glial and neuronal membranes. Elevated of glutamate level extracellularly result in dysfunction of calcium homeostasis, and glutamate excitotoxicity, activation of proteases enzyme, increased production of nitric oxide, cytotoxic transcription factor levels elevation, and enhanced free radicals' formation that may after lead to neuronal death (26). Two subclasses of glutamate transporters are: sodium dependent excitatory amino acid transporters (EAATs) and vesicular glutamate transporters (VGLUTs). Additionally, there is antiporter system of cysteine-glutamate that monitor cysteine -glutamate exchange at the synapse (27).

### 3.1 Excitatory Amino Acid Transporters (EAATs)

Regulating glutamate homeostasis also happened by EAATs are membrane bound pumps protein, which are responsible for preserving a low physiological extracellular glutamate level and it is removed fastly from synaptic

cleft by (EAATs) (28) and are present in both glial cells and presynaptic neurons (29). Glutamate is influx along with one proton and three sodium ions then followed by efflux of one potassium ion (30). this receptor depends on electrochemical gradient. EAATs are sub-divided into five types have been found in human and rodent brains (31).

### 3.2 Vesicular Glutamate Transporters (VGLUTs)

VGLUTs are a family of protein pump neurotransmitter transporter liable for move and uptake of glutamate into presynaptic vesicles for storage. This process occurs by a proton-dependent electrochemical gradient that found on the vesicle membrane and depends on the electrical potential gradient created by a vacuolar-type ATPase (32). VGLUT1, VGLUT2, and VGLUT3 are three iso-forms of VGLUTs have been defined in the mammalian central nervous system (33).

### 3.3 Antiporter of Cysteine-Glutamate system

The antiporter system is sodium ($Na^+$) -independent a plasma membrane-bound, that shuffle extracellular cysteine with intracellular glutamate and act as an origin of release the non-vesicular glutamate (34). This system finds as two separate proteins: the heavy chain 4F2 that is familiar for several amino acid transporters and the light chain cysteine-glutamate exchanger (xCT) that is alone to the cysteine-glutamate antiporter which promotes uptake of cysteine and glutathione biosynthesis, as a result is protecting against oxidative stress (35). As alike EAATs, this antiporter system is located through-out the body on different cell and preferentially on glia in the brain. Moreover, this antiporter supplies tone to mGluRs and amino acid cysteine for synthesis of glutathione, so prevent formation of free radicals and oxidative stress (27, 36). Restitution activity of this antiporter occur by either systemic administration of N-acetyl cysteine or by intracranial perfusion of cysteine has been demonstrate to diminish of cocaine and alcohol seeking in rat patterns (37). Further studies showed that ceftriaxone therapy rejuvenate both levels of GLT1 and xCT, which in sequence prevent reversion to cocaine and alcohol-seeking behavior (38, 39). The Glutamatergic system is shown in (Figure 2) (40).

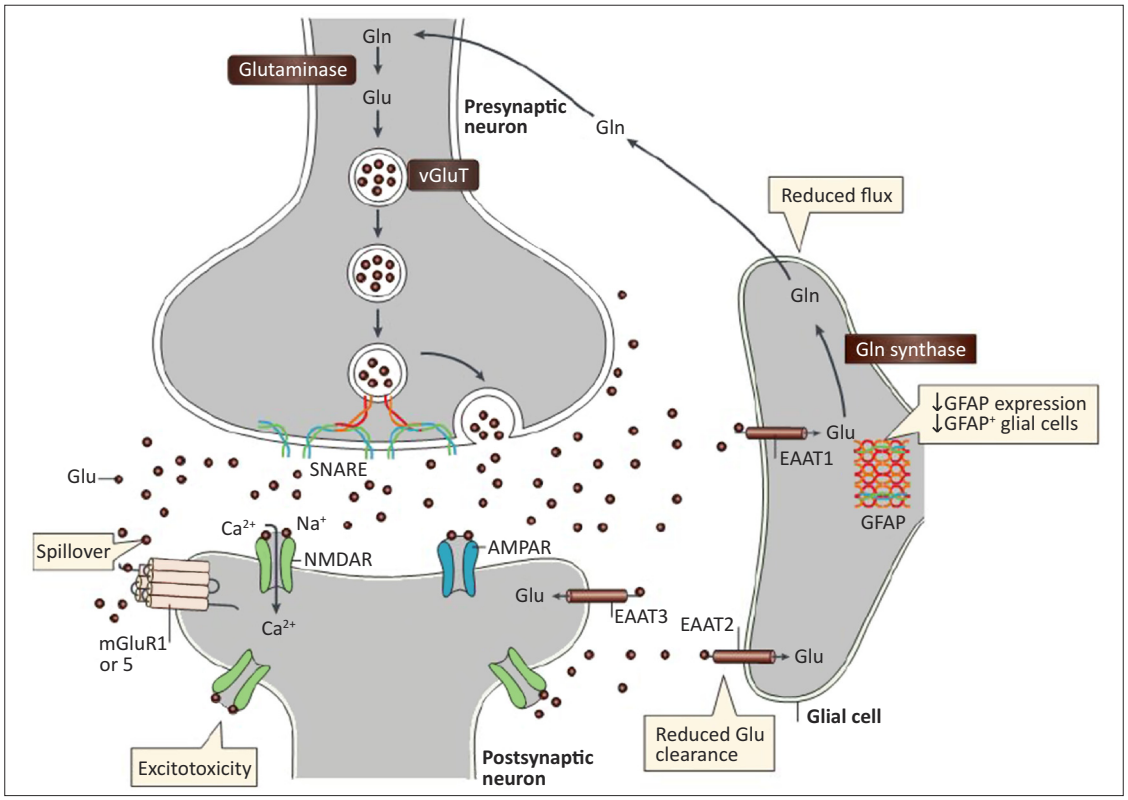


**Figure 2.** Glutamatergic system (40).

## 4. Reuptake of Glutamate in Alcohol Dependence.

Excitotoxicity is mediated by acute elevation of extracellular glutamate level which has a critical role in secondary injuries development that occur following traumatic brain injury, ischemia and several other neurodegenerative disorders (41). Elevated level of extracellular/intracellular glutamate can be regulated by Glial sodium dependent transporters: GLAST (EAAT1): which are in the membrane of glia and pre-synaptic neurons. and GLT1 (EAAT2), and about less than 5% of all up taking glutamate into astrocytes is intermediated by chloride-dependent, $Na^+$-independent antiporters. At least 90% of extracellular glutamate are particularly displace by GLT1 (42). Downregulation or dysfunction of EAAT2 lead to Impaired in up taking of glutamate and results in many neurological disorders, including ischemic stroke, Alzheimer's disease, epilepsy, Huntington's disease, ischemia Amyotrophic Lateral Sclerosis (ALS), and hepatic encephalopathy (43). Previously, we explain that significant down-regulation in expression of GLT1 in the prefrontal cortex in P rats following chronic exposure to alcohol (44). As a compared to non-alcoholic individuals, many studies show that a significant decrease in EAAT1 and EAAT2 levels in the basolateral amygdala in postmortem human alcoholic brains (45). The substantial inherent potential's role of glutamate transporters to regulate synaptic level of glutamate, particularly GLT1, represent potential molecular target for alcohol dependence treatment (40).

## 5. Pharmacotherapy

### 5.1 Glutamate neurotransmission for alcohol dependence as a targeting current pharmacotherapy

Targeting multiple different systems as recent possible therapeutics for alcohol dependence, because of unknown the action nature of alcohol in brain. Generally, (naltrexone) dampening the rewarding effects of alcohol use, (disulfiram) producing ethanol an aversion effect, (acamprosate) restore hemostasis equilibrium between excitatory and inhibitory neurotransmission in the CNS (46).

#### *Acamprosate*

Acamprosate consider is an available FDA-approved therapy for alcohol dependence. Ideally, targeting of drugs to the mesocorticolimbic reward pathway and counteracting chronic ethanol exposure effects and induction adaptation effects on brain would allow an achievable several pharmacological solutions. Acamprosate is FDA-approved drug for treatment of alcohol dependence. It is a synthetic GABA analogue. It acts as an NMDA receptor antagonist, so counteracting the chronic exposure of alcohol and increase glutamate concentration and precipitate of a hyper-glutamatergic state, which occur during episodes of alcohol withdrawal effect (46). Acamprosate had no effect on $GABA_A$ receptor-mediated postsynaptic inhibitory currents effect in the rat nuclear accumbens or on recombinant human $GABA_A$ receptors, but it may influence $GABA_A$ neurotransmission by inhibition presynaptic $GABA_B$ receptors which affect GABAergic neurotransmission (47). Many studies suggest that treatment with acamprosate is moderately effective or ineffective in multi- clinical trial centers and applies its effects primarily via modulating glutamatergic not GABAergic transmission. In fact, several mechanisms were described but the major one of acamprosate action is to normalize extracellular glutamate concentration (hyper-glutamatergic) in several regions of brain reward, including (NAc) and so debilitate alcohol dependence. (48, 49).

#### *Topiramate*

Topiramate is an anti-epileptic FDA- approved drug, attenuates amino-3- hydroxy-5-methylisoxazole-4-propionic acid (AMPA) and kainate glutamate receptors also diminish release of dopamine in mesolimbic system and because of this dual effect of topiramate in decreases withdrawal syndrome and craving aid in decreased the relapse in alcohol dependence. Also it has been shown lowering intaking of alcohol due to its glutamatergic neurotransmission modulation (50, 51).

Principally, topiramate be effective in decreasing drinking of alcohol and inhibiting return in human subjects (52, 53). Up to (75 mg/day) of topiramate is begin an aid to psychotherapeutic treatment, is tolerated well and effective in decreasing craving of alcohol, depression and anxiety of alcohol withdrawal symptoms. Additionally, topiramate aids to cease drinking through the first 16-week post detoxification period (54).

***Baclofen***

Baclofen is a GABA receptor agonist; it is not an approved FAD- drug for alcohol use disorder (AUD) treatment therefore its off-label use in this indication. 30–80 mg/day used fixed dosing in most trials. The maintenance dose about from 30 to more than 300 mg/day (55).

In a few clinical researches have demonstrate that anti-craving and anxiolytic properties of baclofen, may can maintain abstinence and inhibit adverse effects of AUD particularly depressant effects of central nervous system and prevent recovery in patients with AUD. The safety using of a high dose of baclofen is not demonstrated until now, and a latest study from the French Health Agency demonstrate a high doses of baclofen cause duplicating of mortality rate which led to limitation dose of baclofen in AUD to 80 mg/day. Other available data suggests that <80 mg/day of baclofen are well tolerated and safe and can assist in maintain abstinence and inhibit recovery in patients with alcoholic liver disease due to its limited hepatic metabolism (56).

**5.2 GLT1 Up- regulators: Potential targets therapy for AUD**

***Ceftriaxone***

Ceftriaxone is a semi-synthetic third-generation of cephalosporin antibiotic with a broad spectrum activity against bacterial infection and antimicrobial agent. which can be taken either intramuscularly or intravenously, and has a high affinity of protein binding with the longest-half-life so, it is administrable as a single dose-daily (57). It was known to be a potent modulator (i.e., elevation) glutamate transporter 1 (GLT1) (58). Studies have shown a reduction in alcohol consumption in alcohol-preferring (p) rats' model due to activation and upregulation of GLT1 (59).

It was shown that single I.P. injection of 200mg/kg/day of ceftriaxone in Huntington's disease mouse model for five days' cause elevate in uptake of glutamate in striatum coronium, which is a first target for cortical glutamatergic inputs. Also, the neuroprotective effect of ceftriaxone in models with motor neuron degeneration and ischemic injury in which neuro-toxic levels of glutamate reach by enhancing GLT-1 expression and promoting its ability to clear the glutamate from synaptic gap (60), thus; a direct effect of ceftriaxone on glutamate homeostasis occur by up-regulation of GLT1 has a great benefit to alleviate hyperglutametergic states or disorders such as ischemic neuronal damage (61).

In a study shows that treatment with (200 mg/kg/day) of ceftriaxone during abstinence give statistically significant decrease consumption of ethanol when re-exposed to ethanol as compared to the saline treated P rats group. This reduction in ethanol intaking in P rats was observed from Day (2- 9). At a higher dose of ceftriaxone shows attenuation effect in the recovery of drinking in chronic ethanol intake model (62). Following ceftriaxone treatment, the depletion of ethanol consumption was related with GLT1 upregulation in the mesocorticolimbic region (Acb and PFC). Furthermore, ceftriaxone administration by I.p., shows be affected in lowering ethanol withdrawal and relapse- drinking like behaviors via upregulation of glutamate transporter EAAT2 (63, 64).

***Neuroimmunophilin GPI-1046***

GPI-1046, 3-(3-pyridyl)-1-propyl (2S)-1-(3,3-dimethyl-1,2- dioxopentyl)-2-pyrrolidinedinecarboxylate, is an immunophilin synthetic ligand and analog of FK506. Immunophilin ligand which is a macrolide antibiotic with immunosuppressive characteristics (65). It's mode of action is similar to cyclosporine A but, structurally unrelated to it. FK506 effect through impairment expression of gene in target cells. FK506 binding protein (FKBP) is the first as the receptors of immunosuppressant drugs were described in clinical settings to prevent transplantation and graft rejection. FK506 is usually referred as a calcineurin inhibitor. The drug inhibits calcium-dependent events via interact with the major $Ca^{2+}$ release channels of the sarcoplasmic reticulum (SR) and ryanodine receptors (RyRs) (66).

Along with neuroprotective properties. Up regulation effect of GPI-1046 on glutamate transporter 1 (GLT1) expression in PFC and NAc both *in vivo* and *in vitro* shows attenuate in ethanol intake (67). Recent reporters showed that giving of GPI-1046 in P male rats decrease intake of ethanol in a dose-dependent manner. The higher dose (20 mg/kg) of GPI-1046 decreased 70% in ethanol intake dramatically from an average of (7 g/kg -2g/kg) of body weight/day (68).

### *MS-153*

It is (R)-(–)- 5-methyl-1-nicotinoyl-2-pyrazoline (MS-153) synthetic compound decreased intaking of alcohol in male P rats' models, due to upregulation of GLT1 expression in nucleus accumbens (NAc) but not in the prefrontal cortex (PFC). Intraperitoneal administration of 50 mg/kg of MS-153 in P male rats shows reduction in ethanol intake. This reduction effect of MS-153 was long-lasting time over 10 days' post-treatment (69).

Significantly, down-regulatory expression effect of light chain cysteine-glutamate exchanger (xCT) and GLT1 by ethanol consumption on p male rats exposed group, MS-153 will be regularizing of these glutamate transporters expression (up-regulated GLT-1 activity) in both hippocampus and amygdala of treated P rats' group as compared to vehicle control group (70).

## 6. Conclusion

A number of neuromodulators and neurotransmitters in the CNS are affecting by alcohol consumption, including serotonin, dopamine, and GABA. Glutamate excitatory neurotransmitter has a critical affect in expression and development of alcohol dependence. Particularly, neuroplastic alterations in CNS circuitry are often associated with glutamatergic activity variations. The existing researches illustrate that chronic alcohol exposure cause in an obvious elevate in activity of glutamatergic neurotransmissions within these neuronal circuits. So, the pharmacological therapies which can prevent the hyper glutamatergic activity can help in treatment of alcohol dependence. Physically and/or functionally compounds that upregulate glutamate transporters, particularly GLT1, are optimal applicant for more additional examinations and researches.

## Conflict of Interest

Regarding the publication of this article, the authors declare that there is no conflict of interest.

## Adherence to Ethical Standards

This review article did not include performance of any studies by the authors on animals or human participants.

## References

1. Airapetov M, Eresko S, Lebedev A, et al. The role of Toll-like receptors in neurobiology of alcoholism. BioScience Trends. 2021;15(2):74-82.
2. Ahmad FB, Anderson RN. The Leading Causes of Death in the US for 2020. AMA. 2021;325(18):1829-1830.
3. Manthey J, Hassan SA, Carr S, et al. What are the Economic Costs to Society Attributable to Alcohol Use? A Systematic Review and Modelling Study. PharmacoEconomics. 2021:39(7)809–822.
4. Nadkarni A, Endsley P, Bhatia U, et al. Community detoxification for alcohol dependence: a systematic review. Drug and Alcohol Review. 2017;36(3):389–399.
5. Sinclair JMA, O'Neill A. Update on the management of alcohol use disorders. BJPsych Advances .2020;26(2):82-91.
6. Oreland L, Lagravinese G, Toffoletto S, et al. Personality as an intermediate phenotype for genetic dissection of alcohol use disorder. J Neural Transm.2018;125(1):107–130.
7. Rubens M, Ramamoorthy V, Attonito J, et al. A review of 5-HT transporter linked promoter region (5-HTTLPR) polymorphism and associations with alcohol use problems and sexual risk behaviors. J Comm Genet. 2016;7(1):1–10.
8. Gortney JS, JRaub JN, Patel P. Alcohol withdrawal syndrome in medical patients. Cleveland Clinic Journal of Medicine. 2016;83(1):67-79.
9. Olivier George. Individual differences in the neuropsychopathology of addiction. Dialogues Clin Neurosci. 2017;19(3):217–229.
10. Singh AK. Alcohol Interaction with Cocaine, Methamphetamine, Opioids, Nicotine, Cannabis, and γ-Hydroxybutyric Acid. Biomedicines 2019;7(1):16.

11. LCarton L, Auger F, Kyheng M, et al. Dose-dependent metabolite changes after ethanol intoxication in rat prefrontal cortex using in vivo magnetic resonance spectroscopy. Scientific Reports. 2019;9:(10682):1-8.
12. Tabakoff B, Hoffman PL. The neurobiology of alcohol consumption and alcoholism: an integrative history. Pharmacol. Biochem. Behav. 2013;113(15):20–37.
13. Sarawagi A, Soni ND, Patel AB. Glutamate and GABA Homeostasis and Neurometabolism in Major Depressive Disorder. Front Psychiatry 2021;27(12):6378.
14. Volman SF, Lammel S, Margolis EB, et al. New insights into the specificity and plasticity of reward and aversion encoding in the mesolimbic system. J. Neurosci. 2013;33(45):17569–17576.
15. Brooks AM, Berns GS. Aversive stimuli and loss in the mesocorticolimbic dopamine system. Trends in Cognitive Sciences. 2013;17(6):281-286.
16. Babaev O, Chatain CP, Krueger-Burg D. Inhibition in the amygdala anxiety circuitry. Exp Mol Med. 2018;50(4):18.
17. Alasmari F, Goodwani S, Robert E. et al. Role of glutamatergic system and mesocorticolimbic circuits in alcohol dependence. Prog Neurobiol. 2018;171:32-49.
18. Rao PSS, Bell RL, Engleman EA, et al. Targeting glutamate uptake to treat alcohol use disorders. Front. Neurosci. 2015;9(144).
19. Youn DH, Gerber G, Sather WA. Ionotropic glutamate receptors and voltage-gated $Ca^{2+}$ channels in long-term potentiation of spinal dorsal horn synapses and pain hypersensitivity. Neural Plast. 2013;2013(654257). 19 pages.
20. Crupi R, Impellizzeri D, Cuzzocrea S. Role of Metabotropic Glutamate Receptors in Neurological Disorders. Front. Mol. Neurosci.2019;12(20):1-11.
21. Bell RL, Hauser SR, McClintick J, et al. Ethanol-Associated Changes in Glutamate Reward Neurocircuitry: A Minireview of Clinical and Preclinical Genetic Findings. Prog Mol Biol Transl Sci. 2016;137:41–85.
22. Obara I, Bell RL, Goulding SP, et al. Differential effects of chronic ethanol consumption and withdrawal on homer/glutamate receptor expression in subregions of the accumbens and amygdala of P rats. Alcoholism: Clinical and Experimental Research. 2009;33(11):1924-34.
23. Zhu W, Bie B, Pan ZZ. Involvement of non-NMDA glutamate receptors in central amygdala in synaptic actions of ethanol and ethanol-induced reward behavior. Journal of Neuroscience. 2007;27(2):289-98.
24. Marszalek-Grabska M, Smaga I, Surowka P. Memantine Prevents the WIN 55,212-2 Evoked Cross-Priming of Ethanol-Induced Conditioned Place Preference (CPP). Int. J. Mol. Sci. 2021;22(15):7940.
25. Trantham-Davidson H, Chandler LJ. Alcohol-induced alterations in dopamine modulation of prefrontal activity. Alcohol. 2015;49(8):773-779.
26. Kirdajova DB, Kriska J, Tureckova J. Ischemia-Triggered Glutamate Excitotoxicity from the Perspective of Glial Cells. Front. Cell. Neurosci.2020;14(51).
27. Bridges RJ, Natale NR, Patel SA. System xc-cystine/glutamate antiporter: an update on molecular pharmacology and roles within the CNS. British journal of pharmacology. 2015;165(1):20-34.
28. Alleva C, Machtens JP, Kortzak D, et al. Molecular Basis of Coupled Transport and Anion Conduction in Excitatory Amino Acid Transporters. Neurochemical Research. 2021;46(2):1-14.
29. Gonçalves-Ribeiro J, Pina CC, Sebastião AM, et al. Glutamate transporters in hippocampus: not just prevention of excitotoxicity. Frontiers in cellular neuroscience. 2019;(13):357.
30. Hubbard JA, Binder DK. Glutamate Metabolism. Astrocytes and Epilepsy Book. Chapter 9. 2016; 97-224.
31. Fontana ACK. Current approaches to enhance glutamate transporter function and expression. J. Neurochem. 2015;134(6):982–1007.
32. Martineau M, Guzman RE, Fahlke C. VGLUT1 functions as a glutamate/proton exchanger with chloride channel activity in hippocampal glutamatergic synapses. Nature Communications.2017;8(1):2279.
33. El Mestikawy S, Wallén-Mackenzie Å, Fortin GM, et al. From glutamate co-release to vesicular synergy: vesicular glutamate transporters. Nature Reviews Neuroscience. 2011;12(4):204-216.
34. Koppula P, Zhang Y, Zhuang L, et al. Amino acid transporter SLC7A11/xCT at the crossroads of regulating redox homeostasis and nutrient dependency of cancer. Cancer Commun. 2018;38(1):12.
35. Liu L, Liu R, Liu Y, et al. Cystine-glutamate antiporter xCT as a therapeutic target for cancer. Cell Biochem Function. 2021;39(2):159-345.
36. Matuz-Mares D, Riveros-Rosas H, Vilchis-Landeros MM. Glutathione Participation in the Prevention of Cardiovascular Diseases. Antioxidants 2021;10(1220):1-19.
37. Smaga I, Frankowska M, Filip M. N-acetylcysteine in substance use disorder: a lesson from preclinical and clinical research. Pharmacological Reports. 2021;73(5):1205–1219.

38. Sari Y, Smith KD, Ali PK. Upregulation of GLT1 attenuates cue-induced reinstatement of cocaine-seeking behavior in rats. Journal of Neuroscience. 2009;29(29):9239-9243.
39. Knackstedt L A, Melendez RI, Kalivas PW. Ceftriaxone restores glutamate homeostasis and prevents relapse to cocaine seeking. Biol. Psychiatry 2010;67(1):81–84.
40. Rao PS, Sari Y. Glutamate transporter 1: target for the treatment of alcohol dependence. Current medicinal chemistry. 2012;19(30):5148-5156.
41. Verma M, Wills Z, Chu CT. Excitatory dendritic mitochondrial calcium toxicity: implications for Parkinson's and other neurodegenerative diseases. Front. Neurosci. 2018;12:523.
42. GParkin GM, Udawela M, AGibbons A. Glutamate transporters, EAAT1 and EAAT2, are potentially important in the pathophysiology and treatment of schizophrenia and affective disorders. World J Psychiatry. 2018;8(2):51–63.
43. Anna R. Malik AR, Willnow TE. Excitatory Amino Acid Transporters in Physiology and Disorders of the Central Nervous System. Int. J. Mol. Sci. 2019;20(22):5671.
44. Sari Y, Sreemantula SN, Lee MR, et al. Ceftriaxone treatment affects the levels of GLT1 and ENT1 as well as ethanol intake in alcohol-preferring rats. Journal of Molecular Neuroscience. 2013;51(3):779-787.
45. Kryger R, Wilce PA. The effects of alcoholism on the human basolateral amygdala. Neuroscience. 2010;167(2):361-371.
46. Yahn SL, Watterson LR, Olive MF. Safety and Efficacy of Acamprosate for the Treatment of Alcohol Dependence. Substance Abuse: Research and Treatment. 2013;7(6):1–12
47. Kalk NJ, Lingford-Hughes AR. The clinical pharmacology of acamprosate. Br J Clin Pharmacol. 2014;77(2):315-323.
48. Ho AM, Qiu Y, Jia YF, et al. Combined effects of acamprosate and escitalopram on ethanol consumption in mice. Alcohol Clin Exp Res. 2016;40:1531–1539.
49. Sari Y. Commentary: Targeting NMDA Receptor and Serotonin Transporter for the Treatment of Comorbid Alcohol Dependence and Depression. Alcohol Clin Exp Res. 2017;2 (1):1–4.
50. Jose NA, Yadav P, Kapoor A, et al. Comparison between baclofen and topiramate in alcohol dependence: A prospective study. Ind Psychiatry J. 2019;28(1):44–50.
51. D'Souza MS. Glutamatergic transmission in drug reward: implications for drug addiction. Front. Neurosci. 2015;5(9):404.
52. Morley KC, Kranzler HR, Luquin N, et al. Topiramate versus naltrexone for alcohol use disorder: study protocol for a genotype-stratified, double-blind randomised controlled trial (TOP study). Trials.2018;19(1):443.
53. Baltieri DA, Daro FR, Ribeiro PL, et al. Comparing topiramate with naltrexone in the treatment of alcohol dependence. Addiction. 2008; 03(12):2035–2044.
54. Paparrigopoulos T, Tzavellas E. Treatment of alcohol dependence with low-dose topiramate: an open-label controlled study. BMC Psychiatry. 2011;11(41).
55. Agabio R, Sinclair JM, Addolorato G, et al. Baclofen for the treatment of alcohol use disorder: The Cagliari Statement. Lancet Psychiatry. 2018;5(12):957-960.
56. de Beaurepaire R, Sinclair JMA, Heydtmann M. review article: The Use of Baclofen as a Treatment for Alcohol Use Disorder: A Clinical Practice Perspective. Frontier in psychiatry. 2019;9:(708).
57. Parmar PM, Solanki VV, Barvaliya MJ, et al. Cephalosporins Associated Pseudomembraneous Colitis in an Elderly Male Patient - A Case Report. Curr Drug Saf. 2017;12(3):205-207.
58. Smaga I, Fierro D, Mesa J, et al. Molecular changes evoked by the beta-lactam antibiotic ceftriaxone across rodent models of substance use disorder and neurological disease. 2020;115:116-130.
59. Das SC, Yamamoto BK, Hristov AM, et al. Ceftriaxone attenuates ethanol drinking and restores extracellular glutamate concentration through normalization of GLT-1 in nucleus accumbens of male alcohol preferring rats. Neuropharmacology. 2015;97:67–74.
60. Xian XH, Gao JX, Qi J. Activation of p38 MAPK participates in the sulbactam-induced cerebral ischemic tolerance mediated by glial glutamate transporter-1 upregulation in rats. Scientifc Reports. 2020;10(20601):1-11.
61. Bajrektarevic D, Nistri A. Ceftriaxone-mediated upregulation of the glutamate transporter GLT-1 contrasts neurotoxicity evoked by kainate in rat organotypic spinal cord cultures. Neurotoxicology .2017;60,34–41.
62. Rao PS, Sari Y. Effectiveness of ceftriaxone treatment in preventing relapse-like drinking behavior following long-term ethanol dependence in P rats. Journal of addiction research & therapy. 2014;5(2).
63. Qrunfleh AM, Alazizi A, Sari Y. Ceftriaxone, a beta-lactam antibiotic, attenuates relapse-like ethanol-drinking behavior in alcohol-preferring rats. J. Psychopharmacol. 2013;27(6):541–549.

64. Abulseoud OA, Camsari UM, Ruby CL, et al. Attenuation of Ethanol withdrawal by ceftriaxone-induced upregulation of glutamate transporter EAAT2. Neuropsychopharmacology.2014;39(7):1674–1684.
65. Cheung MY, Auyeung WK, Li KP. A Rice Immunophilin Homolog, OsFKBP12, Is a Negative Regulator of Both Biotic and Abiotic Stress Responses. Int. J. Mol. Sci. 2020;21(22):8791.
66. Tong M, Jiang Y. FK506-Binding Proteins and Their Diverse Functions. Curr Mol Pharmacol. 2015;9(1):48–65.
67. Sari Y. Role of glutamate transporter 1 in the attenuation of alcohol intake. Front. Neurosci.2014;8(8):200.
68. Sari Y, Sreemantula SN. Neuroimmunophilin gpi-104 reduces ethanol consumption in part through activation of glt1 in alcohol-preferring rats. Neuroscience.2012;227:327-335.
69. Alhaddad H, Kim NT, Althobaiti YS, et al. Effects of MS-153 on chronic ethanol consumption and GLT1 modulation of glutamate levels in male alcohol-preferring rats. Frontiers in behavioral neuroscience.2014;8:366.
70. Fontana AC, Fox DP, Zoubroulis A. Neuroprotective Effects of the Glutamate Transporter Activator (R)-(-)-5-methyl-1-nicotinoyl-2-pyrazoline (MS-153) following Traumatic Brain Injury in the Adult Rat. J. Neurotrauma. 2016;33(11):1073-83.