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The Effects of Concomitant Alcohol and Benzodiazepines on the Excitatory and Inhibitory Neurotransmitters and Its Implication in Neuronal Disorders

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Authors' contributions

This work was carried out in collaboration between all authors. All authors contributed for the study of literature. Author AJR wrote the manuscript. All authors read and approved the final manuscript.

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ABSTRACT

Concomitant consumption of ethanol and benzodiazepines (BZDs) play a significant role in the development of tolerance and physical dependence of BZDs. Adaptations within the glutamatergic system in response to prolonged ethanol exposure may in some respects, stimulate the physiological processes associated with experience-dependent synaptic plasticity. This study aims

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to investigate several changes that occur in central nervous system (CNS) receptors GABA, NMDA, 5-HT-3 (serotonin) and AMPA during concomitant consumption benzodiazepines and alcohol. Published literature provide an evidence of abuse potential of alcohol and its effect on GABAA receptor synaptic plasticity in neuronal disorders. These studies reveal that alterations in synaptic functions are believed to play a major role; although tolerance to alcohol intoxication probably occurs at multiple levels,. In particular, compensatory changes in excitatory NMDA and inhibitory GABA receptors probably contribute to the development of ethanol tolerance. These receptors are the sites of action of a number of drugs including barbiturates, benzodiazepines and anesthetics. The results also reveal contributions by other factors like decreased flux of chloride ion in the channels of chore at the $GABA_A$ and $GABA_B$ receptors, as well as the flux of calcium in NMDA responsible for neuronal and peripheral tissue disorders.

Keywords: GABAA receptor; neuronal disorders; alcohol abuse; benzodiazepines.

1. INTRODUCTION

Alcohol and benzodiazepines are the most frequently abused substances having a societal impact not only in terms of the general health of the population, but also affect all population levels, resulting in loss of productivity costs amounting to billions of dollars each year and long-term side effects. High concentrations of ethanol (100 mmol/L or 460 mg/dL) [1] can lead to mortality in human beings [2].

Chronic ethanol and benzodiazepines consumption are believed to play important roles in the development of tolerance and physical dependence on these drugs [3]. Despite alterations in glutamatergic neurotransmission observed after ethanol exposure, the critical role of glutamatergic neurotransmission in many forms of activity-dependent synaptic plasticity suggests that it may also play a role in long-lasting effects on synaptic efficacy and connectivity [4]. Adaptations within the glutamatergic system in response to prolonged ethanol exposure may in some respects, stimulate the physiological processes associated with experience-dependent synaptic plasticity [5].

There are two types of membrane-bound proteins that are directly affected by relevant concentrations of ethanol: membrane-bound proteins that are ligand-gated ion channels (LGICs) and voltage-dependent calcium channels (VDC) [6].

The LGICs are a family of neurotransmitter receptors widely distributed in the mammalian CNS playing a major role in synaptic transmission and regulation of neuronal excitability. In particular, gamma-aminobutyric acid type A ($GABA_A$), N-methyl-D aspartate (NMDA), glycine [7], α-amino-3-hdroxy-5-methyl-4-isoxazoleppi-onic acid (AMPA) receptor [8], neuronal nicotinic [9] and 5-hydroxytryptamine type 3 (5-HT3) receptors [10-11] are LGICs that have been shown to be directly modulated by ethanol and benzodiazepines.

In this review, we investigated the roles of the ethanol and benzodiazepines on synaptic plasticity systems receptors, as well as how these drugs cause several neuronal disorders. Alcohol modulate these receptors by increasing the influx capacity of chloride ions channel resulting into an increase in the concentration of $GABA_A$ receptor, as well as, glycine receptors [12]. On the other hand, alcohol inhibits NMDA receptors. Furthermore, a combination of alcohol with benzodiazepines, Clonazepam and barbiturates lead to increase in $GABA_A$ receptors potential that provoke the high levels of chloride ion channels opening in $GABA_A$ receptors. Both alcohol, benzodiazepines and barbiturates causes modifications in the $GABA_A$ receptor releasing the opening of channels of chloride ion and are negatively affected by hyperpolarization of the cells leaving a non-excitatory state of the neuronal cell [13].

1.1 $GABA_A$, NMDA and *AMPA* Inhibitory Neurotransmitters

The major excitatory and inhibitory neurotransmitters in the brain are glutamate and gamma-aminobutyric acid type A ($GABA_A$). The most widely distributed and abundant receptor-operated ion channels in the CNS are ionotropic glutamate [N-methyl-D-aspartate-NMDA, (RS)-a-amino-3-hydroxy-5-methyl-4-isoxazole propionic acid (AMPA) and kainate] and $GABA_A$ receptors. Both NMDA and $GABA_A$ receptors are composed of multiple subunit proteins, which are thought to assemble as hetero-pentameric structures that exhibit distinct properties

depending upon the particular subunit composition [14].

GABA is an amino acid inhibitor preset in one-third of the synapses neurons. It is the main inhibitory transmitter inducing CNS inhibition at the presynaptic level [13,15]. The main precursor of GABA is glucose, which is also precursors to glutamine and pyruvate. GABA is obtained from glutamate in a reaction catalyzed by glutamate decarboxylase which has the pyridoxal phosphate as a cofactor. After its synthesis, it is stored in synaptic vesicles through the vesicular transporter of inhibitory amino acids (VIATT). GABA is made by neurons or glial cells that have high glutamate affinity (GAT) transporters in their synaptic membrane [15] as shown in Fig. 1.

Glycine has a more localized action when compared to GABA. About half of the synapses of the spinal cord and brain stem uses glycine as the neurotransmitter. In addition to its inhibitory action at the CNS level, glycine mediates excitatory neurotransmission through the potentiation of glutamate action in NMDA receptors [15-16] as shown in Fig. 2.

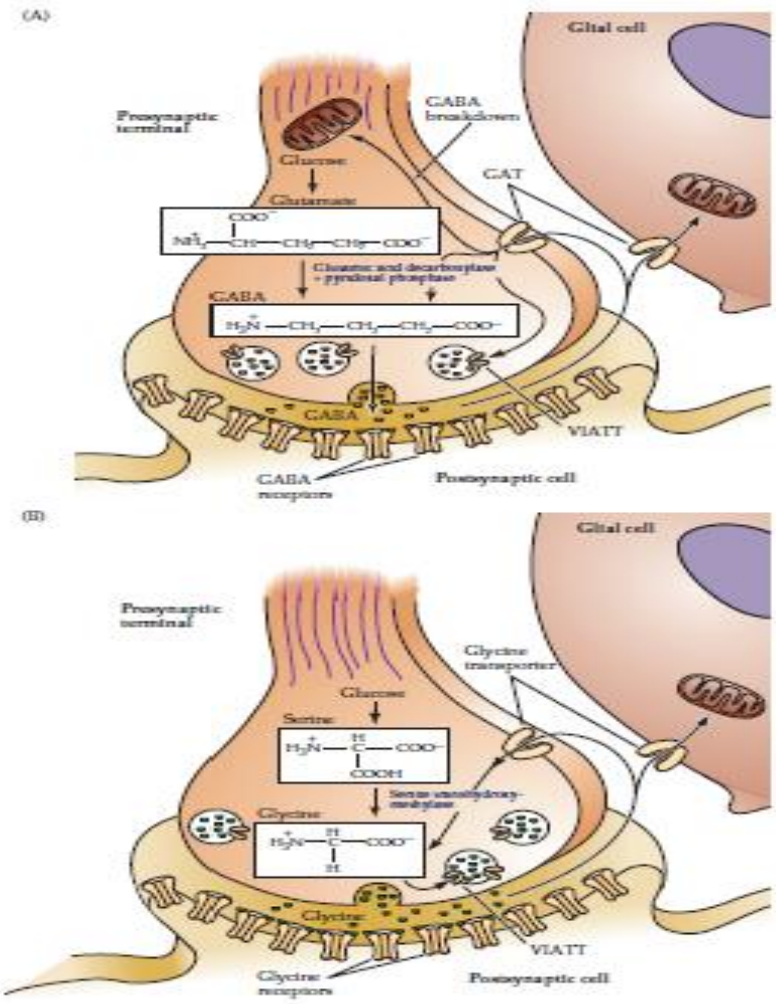

Fig. 1. Synthesis, release, and reuptake of the inhibitory neurotransmitters GABA and glycine. (A) GABA is synthesized from glutamate by the enzyme glutamic acid decarboxylase, which requires pyridoxal phosphate. (B) Glycine can be synthesized by a number of metabolic pathways in the brain, the major precursor is serine. High-affinity transporters terminate the actions of these transmitters and return GABA or glycine to the synaptic terminals for reuse, with both transmitters being loaded into synaptic vesicles via the vesicular inhibitory amino acid transporter (VIATT)

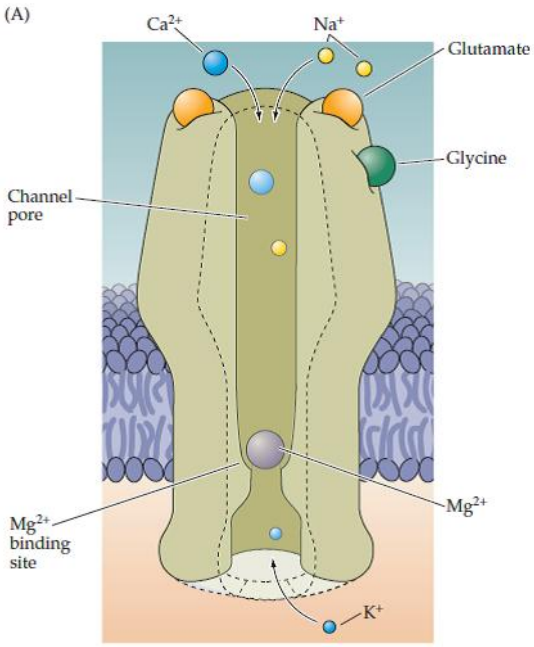

Fig. 2. NMDA and AMPA/kainate receptors. (A) NMDA receptors contain binding sites for glutamate and the co-activator glycine, as well as an Mg2+-binding site in the pore of the channel. At hyperpolarized potentials, the electrical driving force on Mg2+ drives this ion into the pore of the receptor and blocks it

1.2 The Several Types of GABA Receptors and Their Various Synthetic Drug Binding-Sites

GABA possesses three types of receptors: $GABA_A$, $GABA_B$ and $GABA_C$. $GABA_A$ and $GABA_C$ receptors are ionotropics that are permeable to Cl^- ion with negative charge flow inhibiting their postsynaptic neurons; $GABA_B$ receptors are metabotropic. $GABA_A$ receptor is target of drugs such as benzodiazepines, barbiturates and alcohol that binds in different locals of the receptors. They causes the conformational change that allows the entry of Cl^-. Cl-flux induces membrane hyperpolarization, leading to inhibition of action potential of neurons that are target of synthetic drugs [17-18]. The target of the benzodiazepines in the $GABA_A$ ionotropic receptor is not the binding site located between α and β subunits, but a distinct site located in the α and γ subunits [19-20].

Although most $GABA_A$ receptors containing α1, α2, α3 or α5 subunits are sensitive to benzodiazepines (BZD), there is a minority of $GABA_A$ receptors containing α4 and α6 subunits that are insensitive to classical 1,4-benzodiazepines as A class of anxiolytic and hypnotic-sedative drugs [4,21]. $GABA_A$ receptors containing α4 and α6 subunits are sensitive to other classes of gabaergic drugs, such as neurosteroids and alcohol. In addition, there are peripheral benzodiazepine receptors that are not associated with $GABA_A$ receptors as shown in Fig. 3.

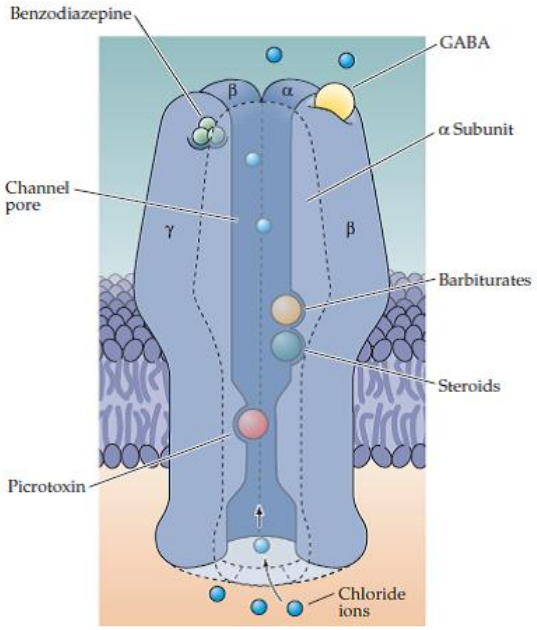

Fig. 3. Ionotropic GABA receptors contain two binding sites for GABA and numerous sites at which drugs bind to and modulate these receptors

$GABA_B$ receptors can stimulate the opening of the K^+ channels which causes the neuron to balance K^+ potential by hyperpolarizing the neuron. This prevents: opening of the sodium channels, triggering of the action potential, opening of the voltage-dependent Ca^{2+} channels, and the release of neurotransmitters. Thus, $GABA_B$ receptors are also considered inhibitory receptors. $GABA_B$ receptors are involved in the actions of ethanol [22], gamma-hydroxybutyric acid (GHB) [23] and possibly pain [24-26].

$GABA_C$ receptor is one of the ligand-dependent ion channels responsible for mediating the effects of gamma-aminobutyric acid (GABA), with minor power inhibitory neurotransmitter than $GABA_A$ in the brain. Though $GABA_C$ receptors are closely related to GABAA receptors and are

expressed in many areas of the brain, $GABA_C$ receptor has a high degree of expression in the retina [17-18]. $GABA_C$ as $GABA_A$, allows increase in Cl^- channel thereby causing hyperpolarization of neuronal cell, however, after stimulation by GABAc, the chloride flux produced by the $GABA_C$ receptor is slow, therefore more time-consuming initiation. $GABA_A$ receptor promote the ions faster and therefore has a shorter duration [27].

1.3 The Effect of the Alcohol in the NMDA and *AMPA* Inhibitor

The NMDA receptors are heterotetrameric protein complexes that form ligand-gated ion channels composed of at least one NR1 subunit and a combination of NR2A-D and NR3A or 3B subunits [28-30]. In addition, amino acids such as D-serine and glycine act as co-agonists at the NMDA receptor and are stimulated by glutamate. The NR2 subunits contains the glutamate-binding domain, whereas the NR1 subunit contains the glycine-binding dopamine. Under resting conditions, the NMDA receptor channel pore is blocked by Mg^{2+} ions, but once the depolarization of the membrane is established with the opening of AMPA receptor channels, the Mg^{2+} block is removed, allowing the influx of cations, initially with Ca^{2+} ions, then followed by K^+ and Na^+ ions. Polyamines modulates the activity of NMDA and are inhibited by Zn^{2+} ions. Once thought to be exclusively located on neurons, NMDA receptors recently was expressed on glial cells including microglia, astrocytes and oligodendrocytes. NMDA receptor subunits were found to exist on presynaptic terminals [29]. The NMDA receptor is involved extensively in the mediation of neural plasticity, as well as, learning and memory processes [30-34].

Alcohol also exerts its inhibitory action on NMDA receptors, decreasing the flow of Ca^{2+} cations through these receptors and by consequence, the communication between the neurons and the structure of the synapses is compromised [35] as showed in Fig. 4.

The acute alcohol consumption decreases glutamergic activity because of its antagonistic effect on NMDA receptors. On the other hand, chronic consumption causes an adaptation of glutamate receptors to the inhibitory effects of alcohol by increasing the sensitivity of the receptors [36-37].

The AMPA receptors are also heterotetrameric protein complexes that form ligand-gated ion channels composed of various subunits termed GluR1-4 (GluRA-D) and GluRδ1 [37-38]. Each GluR subunit contains a binding site for glutamate. Once activated, AMPA receptors are permeable to various cations including Ca^{2+}, Na^+ and K^+. The majority of AMPA receptors in the brain contain GluR2 subunits, which render the channel impermeable to Ca^{2+} [37].

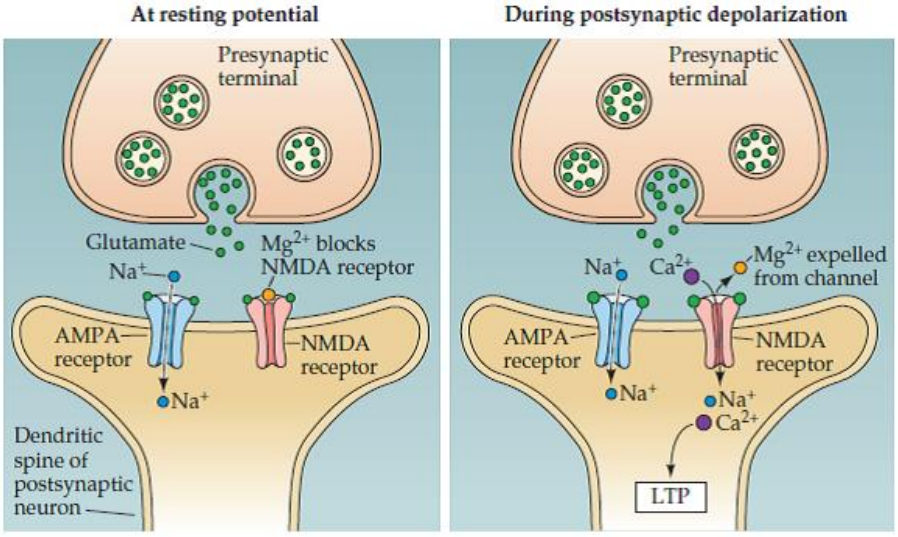

Fig. 4. The NMDA receptor channel can open only during depolarization of the postsynaptic neuron from its normal resting level. Depolarization expels Mg^{2+} from the NMDA channel, allowing current to flow into the postsynaptic cell. This leads to Ca^{2+} entry, which in turn triggers LTP

The AMPA receptor possesses function similar to NMDA receptors; can be modulated in the presence of polyamines. Both NMDA and AMPA receptors are necessary for the induction of many forms of synaptic plasticity such as long-term potentiation (LTP) and long-term depression (LTD) [38].

Kainic acid (KA) receptors are tetrameric protein complexes that form ligand-gated ion channels that are composed of various subunits similar to NMDA and AMPA receptors. These subunits are termed GluR5-7 and KA1 and 2 [8,31]. KA receptors can form homomeric tetramers composed entirely of GluR5, 6 or 7 subunits or heteromeric complexes containing GluR5 or KA subunits. KA receptors are permeable to Na^+ and K^+ ions and like NMDA and AMPA receptors, contributes to excitatory postsynaptic currents. The role of KA receptors in synaptic plasticity is less defined, however, KA receptors are localized in presynaptic membrane where they can modulate the release of neurotransmitter [28].

1.4 Acute, Self-administration and Chronic Effects of Alcohol and Benzodiazepines on $GABA_A$ Receptors

The Acute effects of ethanol on $GABA_A$ receptors are remarkably similar to the effects of benzodiazepines and barbiturates, in that both are modulators of $GABA_A$ receptors. Ethanol is anxiolytic, sedative hypnotic, anticonvulsant and motor in-coordinating [39]. In high concentrations, ethanol acts as an anesthetic and respiratory depressant [4].

Many of these effects of ethanol can be due to interactions with $GABA_A$ receptors [29,31]. The precise mechanism of action for ethanol cannot be inferred from behaviors elicited by administration of systemic ethanol. Scientists believe that the use of $GABA_A$ receptor modulators is the key site for the behavioral effects of ethanol detected in this primary inhibitory neurotransmitter system [23].

Several evidences support the notion that the mesolimbic system, comprising of the nucleus accumbens (NAC), amygdala (AMG), and ventral tegmental area (VTA) is the critical site for self-administration of drugs and abuse of drugs. A central regulatory role of dopaminergic projections in this system suggest that motivational mechanisms is involved in self-administration [15].

Self-administration of several types of drugs, including ethanol, as well as direct electrical stimulation of specific brain regions, suggests that increased dopamine levels in the NAC are key to the initiation of drug self-administration that leads to addiction [15]. There are several interconnections between regions of mesolimbic brain that may provide the neural substrates for development of the dependence of alcohol [18]. While there is a strong evidence suggesting that dopamine neurotransmission in the mesolimbic circuitry is an important common pathway underlying addiction, specific activation of this system may be influenced by the choice of drug [39]. Thus, the increased evidence that $GABA_A$ receptor activation plays a role in self-administration of ethanol. For example, $GABA_A$ receptor antagonists facilitate the acquisition of voluntary ethanol drinking [17] and increase ingestion of ethanol [2].

Benzodiazepine inverse agonists decreases ethanol consumption in non-dependent rats during limited access, suggesting that the involvement of $GABA_A$ receptors in ethanol self-administration is complex and may vary depending on the experimental procedure utilized [40-41]. Persistent consumption of ethanol produces both tolerance and dependence. Tolerance to alcohol is manifested as a reduced behavioral response to alcohol. For example, increased alcohol consumption is necessary to achieve the anxiolytic effects of muscle relaxation [40].

Ethanol dependence increases when there is necessity to drink more doses of alcohol as showed in Fig. 5.

In the absence of alcohol, organism react to several symptoms attributable to CNS such as hyperexcitability, anxiety, dysphoria and increased susceptibility to seizure [4]. The development of ethanol dependence alters many of the properties of $GABA_A$ receptors in the brain. Ethanol tolerance and dependence are associated with decrease in sensitivity of GABAA receptor-mediated responses in the cerebral cortex [39].

1.5 Current Therapies for the Treatment of Alcohol Dependence

Current therapeutics for alcohol abuse include drugs such as disulfiram, naltrexone and acamprosate. Disulfiram inhibits aldehyde dehydrogenase, one of the enzymes involved in

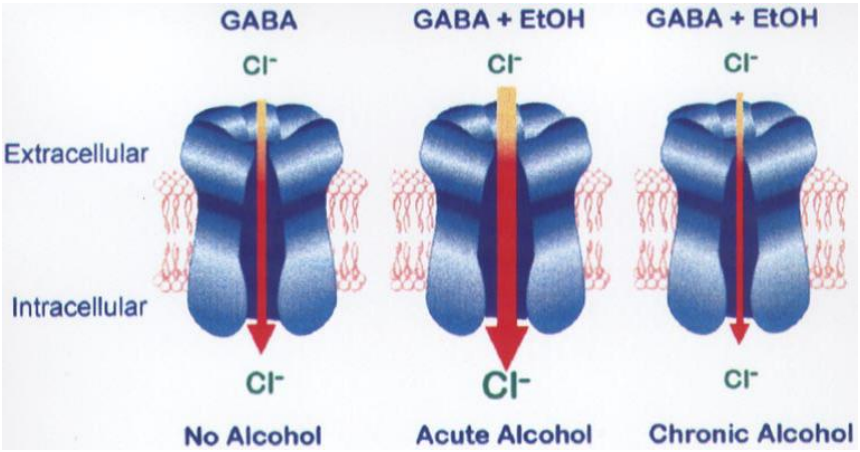

Fig. 5. Representation of $GABA_A$ receptor sensitivity during acute and chronic alcohol administration. Normally, $GABA_A$ receptors, in the presence of GAB_A, will open to allow inßux of Cl- ions along the chloride gradient from outside to inside the cell (leftmost panel), hyperpolarizing the membrane and inhibiting cell Þring. Acute alcohol administration increases the effects of GABA, allowing more Cl- to enter the cell (center). After prolonged ethanol exposure, ethanol and GABA both have reduced effects at the receptor; inhibition is reduced and Cl[ßux is reduced (right panel). Therefore, the inhibitory tone of the neuron is enhanced acutely by ethanol but reduced after prolonged exposure to ethanol

alcohol metabolism, which converts acetaldehyde to acetic acid [42]. The administration of disulfiram in the absence of alcohol have little or no inhibitory effect on aldehyde dehydrogenase. However, consumption of alcohol can lead to increased concentration of acetaldehyde and these results in several unpleasant effects such as tachycardia, nausea, vomiting and hyperventilation, often accompanied by feelings of anxiety or panic due to the toxic effects of acetaldehyde in the organism. This enzyme is essential for detoxification of acetaldehyde to acetic acid [43]. Strong interaction between opioid receptors and alcohol has shown that opioid receptors are involved in the reinforcing effects of chronic ethanol consumption. The naltrexone is an opioid receptor antagonist and its effects on alcohol dependence is that it decreases the desire to consume alcohol. Therefore, Naltrexone is prescribed as an anti-alcohol medication because clinical trials have shown that it helps relieve the urge that alcoholics have to consume ethanol [44].

Acamprosate (N-acetylhomotaurine) is another alternative used as a therapy for alcohol abuse and is best used to maintain abstinence in patients who have stopped drinking alcohol [45]. Acamprosate has a structure similar to GABA and has been shown to interact with presynaptic $GABA_B$ receptors, increasing the flux of chloride ion in the $GABA_B$ receptors from presynaptic terminals leading to hyperpolarization of neuron cell [46]. Additionally, it appears also to inhibit calcium ion influx through voltage-dependent calcium channels and NMDA receptors [47]. This drugs act by reducing dependence on alcohol [48-49].

2. CONCLUSION

Alcohol abuse is a grave problem threatening health of human populace because of the high addiction tendency which often results into several neuronal disorders such as decreased flux of chloride ion in the channels of chore at the $GABA_A$ and $GABA_B$ receptors, as well as the flux of calcium in NMDA. Several drugs, including benzodiazepine, have been synthesized to control alcohol consumption or at least, decrease dependence on alcohol. However, the mixture of alcohol with benzodiazepines leads antagonistic effects on the GABA receptors. Additionally, with the discovery of the strong interaction between opioid receptors and alcohol, some anti-opioid such as Naltrex have been developed to decrease the desire for alcohol consumption. Other anti-abuse agents such as disulfiram, inhibit aldehyde dehydrogenase. The administration of disulfiram in the absence of alcohol causes little or no effect. However, if alcohol is consumed, there is increase in acetaldehyde concentration which results in

several unpleasant effects such as tachycardia, nausea, vomiting and hyperventilation, often accompanied by feelings of anxiety or panic due to the toxic effect of acetaldehyde in the organism. The challenge now is to find more efficient form of treatment for patients that abuse alcohol with/or no use of benzodiazepines in order for them to live a more healthy life.

CONSENT

It is not applicable.

ETHICAL APPROVAL

It is not applicable.

COMPETING INTERESTS

Authors have declared that no competing interests exist.

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