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The Role of Alcohol and the Mechanisms Involved in the Reward Pathway Affecting the Brain: A Comprehensive Review

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Abstract Alcohol addiction is an important social problem prevalent throughout the world. People addicted to alcohol find it very difficult to avoid it, and subsequently, they are prone to health-related complications as a result of excessive alcohol consumption. Alcohol is a psychoactive substance, and its addiction affects the brain. Among people addicted to alcohol, a brain mechanism, known as the reward pathway, is activated. This reward pathway of the brain is further responsible for increased alcohol carving, and subsequently its addiction, and resultant consequences. Although alcohol addiction is seen mostly among men, women are equally predisposed to alcoholism. In the present review, we emphasize the role of the reward pathway of the brain in alcohol addiction, gender disparities, and approaches to managing alcohol-dependent people.

Keywords: *alcohol addiction, reward pathway, brain, gender disparities*

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1. Introduction

Alcohol containing beverages like whiskey, vodka, wine, brandy, and beer, among others contains ethanol which is a psychoactive substance produced by the fermentation of grains, fruits, and other sources of sugar [1]. Ethanol is an alcohol that acts as a central nervous system depressant, and when it is consumed as an alcoholic drink, it is readily absorbed from the stomach, intestines and is distributed throughout the body, thereby combining with the body fluids, and becoming a part of every cell of the body [2].

1.1. Metabolism of Ethanol in Human Body

After consumption as an alcoholic beverage, ethanol is absorbed from the stomach and intestines, and a small quantity is lost/excreted in the form of sweat and urine. The liver plays an important role in the metabolism of absorbed ethanol. In the liver, ethanol is metabolized in a two-step process that is mediated by the enzyme alcohol dehydrogenase and aldehyde dehydrogenase [3].

The two-step pathway involving ethanol metabolism is shown in Figure 1.

The first step is reversible and is carried out by the action of alcohol dehydrogenase in the cytosol [4]. However, some minor actions involving cytochrome P450 2E1 (CYP2E1) and catalase are also noted in the peroxisomes and microsomes [5,6]. The enzyme CYP2E1 is induced by chronic alcohol consumption. It breaks down ethanol and releases Reactive Oxygen Species (ROS), which contributes to creating an oxidative stress condition. The catalase enzyme of microsomes which degrades peroxides into the water helps in the production of acetaldehyde from ethanol in the brain cells [7].

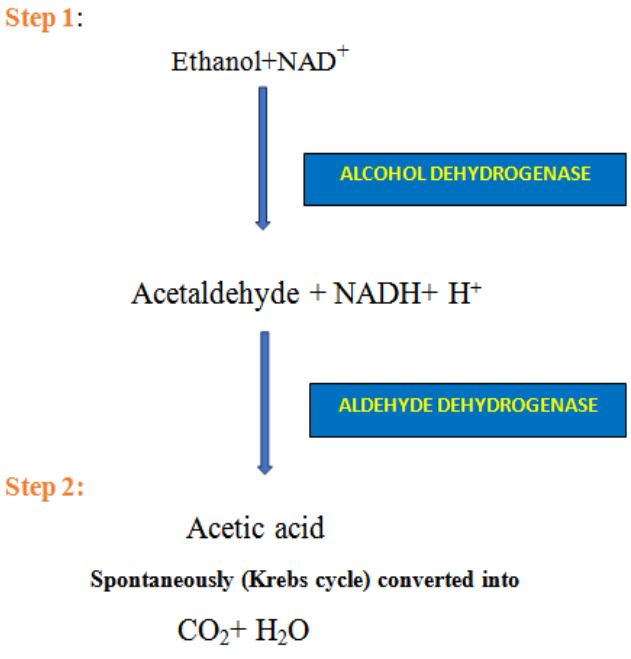

Figure 1.

The acetaldehyde formed in the liver cytosol leaves and moves into the liver mitochondria, where it is acted upon by acetaldehyde/aldehyde dehydrogenase present in the liver mitochondria converting it into acetic acid. The accumulation of acetaldehyde is toxic since it leads to facial flushing, lightheadedness, palpitations, sweating, and generalized hangover symptoms which are collectively called 'alcohol flush reactions' [8]. Thus, the enzyme aldehyde dehydrogenase helps in maintaining low blood acetaldehyde activities.

However, there is limited availability of the enzyme aldehyde dehydrogenase in the liver mitochondria. Therefore, excessive alcohol intake saturates this enzyme and results in the accumulation of acetaldehyde in the bloodstream. The acetic acid formed after alcohol metabolism is further processed in the muscle and heart tissues and converted into acetyl-CoA by the action of the enzyme acyl-CoA synthetase. The acetyl Co-A then enters the Krebs cycle and is further broken down into carbon dioxide and water [9,10].

The increased amounts of NADH generated from the ethanol breakdown by alcohol dehydrogenase will inhibit the process of the Krebs cycle. Hence, acetate formation will not take place from acetaldehyde, which causes this molecule to take an alternative route.

2. Alcoholism and Stages of Alcoholism

Alcoholism is an alcohol use disorder wherein a person develops an uncontrolled addiction/dependence on alcohol. The addiction to alcohol is both physical and emotional, and the affected persons cannot relieve the habit despite their willingness. There are several stages involved before a person becomes dependent on alcohol even after knowing its potential effects on the physical, social, and financial wellbeing.

The stages of alcohol dependence include the first stage, also known as the pre-alcoholic stage. Here, alcohol intake starts as a casual observer or as a stress reliever with a frequent and manageable intake of alcohol. At this stage, the body develops tolerance to alcohol. This later progresses into the second stage called the early alcoholic stage. At this stage, the person develops discomfort and irritability in the absence of alcohol intake. People also develop hiding behavior, tell lies to their loved ones, find excuses to have a drink of alcohol, and obsessed with thoughts of alcohol can be evident. This stage further increases the alcohol tolerance among the affected persons.

At the third stage, which is also called the middle alcoholic stage, alcoholic dependence is clearly noticed by the family and friends. An increasingly irritable nature, arguing nature with the spouse, bodily changes in the form of weight gain or weight loss, unable to work due to hangovers can be evident at this stage. This stage is probably where a person could try and control the alcoholic dependence with help or social support.

Finally, the fourth stage known as the late alcoholic stage is where the person considers alcohol consumption as a priority over the family and friends. Liver cirrhosis and dementia can be seen added to the personality disorders like mistrust etc. This stage is difficult to overcome even with the support of family and friends because of the withdrawal symptoms like tremors, and hallucinations, among others which make them weak [11].

3. Alcoholism and Its Influence on the Reward System of Brain

The reward is a favor given to an individual either in the form of a financial benefit or gift. Rewards are given in recognition of service, efforts, or achievement. The reward system of the brain is a combination of brain structures and neuronal pathways that enables the person to think of a reward, desire, or pleasure. Activating the reward system of the brain modifies learning, affects decision making, and evokes positive emotions like happiness, and pleasure, among others [12].

The reward system of the brain consists of the mesolimbic dopamine pathway that is composed of the Ventral Tegmental Area (VTA) and Nucleus accumbens (NAc). VTA is the area where a bundle of neurons is seen on the floor of the midbrain that is situated next to the substantia nigra (which produces dopamine). VTA consists of several types of neurons but is noted as dopaminergic neurons.

The mesocortical and mesolimbic pathways are the major pathways coming out of VTA. The mesocortical pathway is widespread and participates in human activities such as emotions, motivation, and executive functions, among others. The mesolimbic pathway has diverse actions, and it is majorly involved in the reward execution pathway associated with dopaminergic neurons. Addiction leads to the entry of VTA neurons into the nucleus accumbens, thereby connecting both the regions of the brain [13].

The mesolimbic dopamine system, which is also called the reward system connects the midbrain to the forebrain. The midbrain engages in controlling the movements and error signals to reward prediction, motivation, and cognition. The release of dopamine from the mesolimbic system (VTA) regulates the motivation and desire for rewarding stimuli and reward-related motor functions including learning and seeking pleasure. The rewarding stimuli are the stimuli that the brain interprets as positive and harmless.

Moreover, the reward system of the brain is associated with the activities of dopamine. This affects the pleasure-seeking behavior and activates the rewarding process of the brain. The dopamine released from VTA combines with dopamine receptors and releases or inhibits cyclic AMP (cAMP). The cortical and limbic information can be passed from the NAc shell to the midbrain via dopamine neurons [14,15]

The ventral striatal (voluntary movement controller) region of the brain is called as Nucleus Accumbens (NAc) which is a part of the forebrain. The forebrain plays an important role in pleasure, material behavior, aversion (unpleasant stimuli which change a behavior), and slow-wave sleep (deep sleep with loss of response to external stimuli), among others.

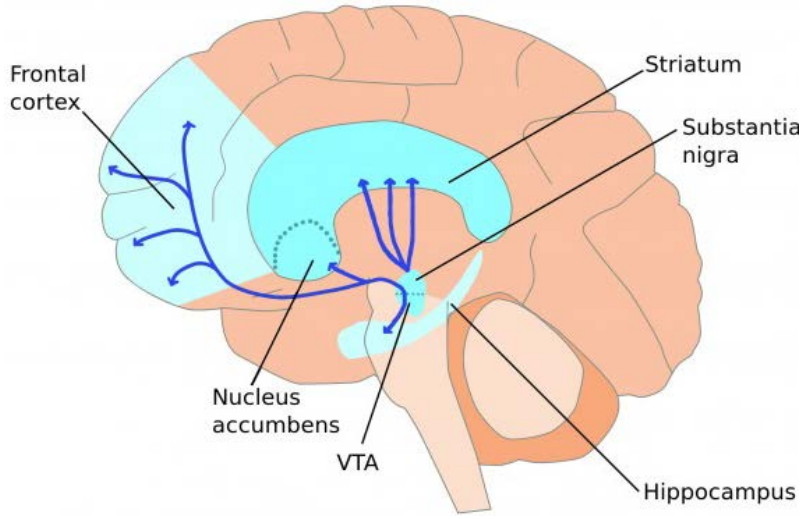

Figure 2. The brain reward pathway (Courtesy: https://sites.bu.edu/bryantlab/dopamine-pathways/)

The VTA of the mesolimbic system projects into the striatal region and activates Gama Amino Butyric Acid (GABA)-energic neurons via D1 and D2 receptors both in ventral and dorsal striatal regions. The NAc core projects into Substantia nigra that participates in the development of reward-seeking behavior, impulsive choice, and conditional responses. On repeated activation of the mesolimbic system, with stimuli like drug abuse including opioids, cocaine, alcohol, etc. the NAc activates the dorsal striatal region via an intrastriatal loop. This transition of stimuli can allow the reward-associated cues to get activated in the dorsal striatal region without the presence of the actual reward itself. This in turn activates carvings and reward-seeking behaviors. The other brain compartments that are associated with the mesolimbic system like the prefrontal cortex (environmental cues related to reward), hippocampus (memories related to reward), amygdala (powerful emotional memories), pleasure centers (reactions from intrinsic rewards) are also involved in the reward system of brain [16,17,18] (Figure 2).

4. Addiction and Reward Pathway

Addiction is a complex condition of the brain which exhibits dependence/compulsion to substances like alcohol, drugs, etc. despite the awareness of the resultant harmful consequences. Addiction increases the carving for substances and activates the reward pathway. The addiction process not only gives rewards but also enables the forebrain to involve in planning, and judgment to seek the reward via the release of dopamine. Thus, substance dependence changes normal regulatory or rechecking functions of the brain, making it more vulnerable to addiction [19].

5. Addiction and Parts of the Brain Affected by the Alcohol Addiction

After ingestion, the alcohol enters the bloodstream and reaches the brain via neurotransmitters which can either increase or decrease brain activity. Unlike other substances of abuse, alcohol addiction affects whole neurotransmitters at the same time. The brain cortex is the first affected region due to alcohol addiction. Normally, the cortex engages in thinking and controlling voluntary movements. However, alcohol addiction confuses and creates a carefree attitude or a no inhibition behavior (terrible jokes, etc.) among affected people.

The release of GABA, which is an inhibitory neurotransmitter creates anxiety, stress, and fear. However, consumption of increased quantities of alcohol interferes with this inhibitory action of GABA on the brain and results in a condition of no fear.

The serotonin released from the brain stem controls anxiety, happiness, and mood. Initially, the drinking habit elevates serotonin levels temporarily. However, excess alcohol intake decreases the activity of serotonin, thereby affecting the person's mood (feeling depressed).

Apart from the cortex, the cerebellum of the brain is affected by alcohol consumption. The cerebellum normally helps in the coordination and balance of the human body. Increased alcohol intake causes altered movements and imbalance among addicted people.

Further, excessive alcohol consumption affects the brain’s hypothalamus and amygdala. The hypothalamus functions in regulating the appetite, body temperature, emotions, pain, and the amygdala control social behavior. Elevated alcohol consumption results in people hurting themselves unknowingly and developing powerful animal instincts. Thus, the brain’s ability to reason is switched off. Finally, Alcohol addiction could result in improper functioning of the brain stem, which causes sleep disorders, irregular breathing, and seizures [20].

6. Mechanism of Action of Released Dopamine

The dopamine released after the activation by alcohol acts via receptors. There are about 5 receptors (D1 to D5) seen on the surface of the Central Nervous System (CNS), and these receptors are G protein-coupled receptors [21]. The D1 receptors are abundantly found as against the rest

of the receptors for dopamine. The D1and D5 receptors are excitatory neurotransmitters whereas D2, D3, and D4 receptors are inhibitory neurotransmitters [22].

Chronic alcoholism inhibits the dopamine transporter (DAT) responsible for removing dopamine from the neural synapse, thus the synapse is flooded with dopamine, thereby increasing the D1 receptors, and suppressing the D2 receptor signaling. This mediates the activation of reward stimuli after excessive alcohol intake [23].

7. Role of Medicine in the Treatment of Alcoholism

The medicine for alcoholism works for people who want to stop drinking. This corresponds to the strong mental status of the individual to avoid alcohol consumption. The drugs for de-addiction influence the psychological changes in the person. Some of the drugs used to treat alcoholism are discussed in the sections below.

7.1. Disulfiram

This drug acts by altering the alcohol metabolism i.e., the first product of alcohol metabolism, the acetaldehyde is not further degraded. This causes the accumulation of acetaldehyde, which leads to side effects, and patients on these drugs show symptoms like headache, nausea, vomiting, sweating, mental confusion, impaired vision, anxiety, etc. The disulfiram does not reduce alcohol cravings (urge for the substance that is withheld) and other subjective states of addiction [24].

7.2. Naltrexone

It reduces cravings and feelings of euphoria associated with the intake of alcohol by blocking opioid receptors. It is not recommended for people with liver failure and side effects of usage of this drug include trouble sleeping, anxiety, nausea, and headache [25].

7.3. Acamprosate

It is a drug used along with counseling sessions as it stabilizes signaling in the brain by disrupting glutamate (alcohol withdrawal). Intake of this drug leads to gastrointestinal problems like diarrhea, allergic reactions, abnormal heart rhythms, headache, insomnia and it should not be given to people with kidney problems or drug allergy history [26,27].

8. Meditation Therapy for Alcoholism

Meditation is a simple but powerful technique for improving individual self-control over substance addiction. Meditation can be defined as a practice where clarity of mind and stability of emotions can be achieved [28]. Since medicine used for alcoholism leads to side effects like headache, nausea, vomiting, craving nature for alcohol, psychosis, and seizures, a combined approach using drugs and meditation is recommended.

Meditation has been shown to decrease beta waves in the brain, especially in the frontal lobe. The Beta waves are the faster brain waves that are engaged in mental activities. Meditation facilitates the development of stable alpha waves in the brain.

Meditation improves focus, creativity (reduced emotions), and productivity (better memory). It controls anxiety (by weakening neural connection in the medial prefrontal cortex) and reduces stress (improved performance) enhanced [29]. Experimental studies have shown that long-term practice of meditation improves the right side of the cerebral cortex. This facilitates people to remain calm in the present situation and not worry about the past and future [30].

Meditation improves grey matter as evident from the results of neuroimaging study conducted on participants after eight weeks of meditation. This has positive implications for improved mental health and better emotional status [31].

9. Gender Discrepancies in Alcohol Addiction

It is observed that alcohol and its addiction are more gender-oriented. This can be attributed to the large amounts of enzyme alcohol dehydrogenase being produced in men as compared to women. This contributes to men tolerating an alcohol consumption of 120ml per day.

Alcohol is stored in body fat (indirectly by activating sex hormones), and women who generally have more body fat, tend to experience alcohol effects faster after alcohol intake.

Women start alcohol consumption to handle stress and anxiety, whereas men take alcohol to handle social situations. Although the alcoholic tendency is more among men, women may be more susceptible to neurological damage and potentially develop Alzheimer's disease [32,33].

In women, estrogen regulates the dopaminergic system even when there is raised endogenous dopamine synthesis. It was observed that alcoholic men have low striatal D2 receptor density making them more vulnerable to alcohol dependence than women [34,35].

Alcoholism shrinks the brain volume and results in cognitive dysfunction. This develops more quickly in women than in men owing to the fast absorption of alcohol into circulation. Neuroimaging studies revealed that both grey and white matter shrinkage is seen more in the female brain, which corresponds to greater short term memory impairment in women as compared to men [36,37].

Given that men and women respond differently to alcohol, alcoholism treatment also needs to consider the gender variabilities related to complications arising from alcohol addiction. Because sex hormones influence neurotransmitter systems, and patterns of behavior, among others, careful considerations are required before treating alcohol-dependent patients [38].

Meditation has shown improvement in positive nature and understandability among women than men in a study conducted among college-going students [39].

It was observed that mindful meditation helps women to internalize the stress response and allows them to be non-reactive, and less self-critical. Meditation also assists women to activate the cognitive region of the brain and sheds their negative effects on subjective approaches. Such negative effects are not observed in men because of the already active cognitive region [40].

Generally, the dopaminergic reward system in women activates prosocial behaviors (like kindness, empathy, helping, sharing, and co-operative). Whereas among men, the reward system triggers selfish benefits. However, in alcoholism due to the blockage of dopamine transporters, women develop selfish nature and men become prosocial (like concern for others, empathy, sharing, co-operating) [41].

10. Conclusion

The thought of alcohol and its consumption makes men happier than women. This points to the fact that some brain signals are involved with the intake of alcohol. The dopaminergic reward pathway of the brain is responsible for feelings like happiness and pleasure. However, this reward pathway is influenced by alcohol addiction. During excessive alcohol consumption, the activities of dopamine are increased at the nerve synaptic region with diminished dopamine transporter activities. The available literature reveals gender disparities concerning alcohol addiction. Although in women, alcoholism is uncommon, addiction to alcohol results in neurotoxicity (Parkinson's and Alzheimer's disease) and brain-related irreparable damages. Since alcoholism affects the brain and neurotransmitters, and because drugs used to treat de-addiction have many side effects, a combined approach using drugs and meditation may be preferred.

References

[1] Clines T (July 2006). "Brew Better Ethanol". Popular Science Online. Archived from the original on 3 November 2007.

[2] Alcohol use and safe drinking. US National Institutes of Health.

[3] Tanaka, Furnika, Shiratori, Yasushi, Yokosuka, Osarnu, et al. Polymorphism of Alcohol drinking behaviour and alcoholic-metabolizing genes affects drinking behaviour and alcoholic liver disease in Japanese Men. Alcoholism: Clinical and Experimental Research. 1997; 21(4): 596-601.

[4] Riveros Rosas H, Julian-Sanchez A, Pina E. Enzymology of ethanol and acetaldehyde metabolism in mammals. Arch. Med. Res. 1997; 28: 453-471.

[5] Lieber CS. Cytochrome P4502E1: its physiological and pathological role. Physiol. Rev.1997; 517-544.

[6] Thurman RG, Handler JA. New perspectives in catalase-dependent ethanol metabolism. Drug Metab. Rev. 1989; 20: 679-688.

[7] Cohen G, Collins M. Alkaloids from catecholamines in adrenal tissue: Possible role in alcoholism. Science. 1970; 167: 1749-1751.

[8] Thomasson HR, Edenberg HJ, Crabb DW, Mai XL, Jerome RE, Li TK, Wang SP, et al. Alcohol and aldehyde dehydrogenase genotypes and alcoholism in Chinese men. American Journal of Human Genetics. 1991; 48(4): 677-81.

[9] Crabb DW, Matsumoto M, Chang D, You M. Overview of the role of alcohol dehydrogenase and their variants in the genesis of alcohol-related pathology. The proceedings of the Nutrition Society. 2004; 63(1): 49-63.

[10] ACSS2 acyl-CoA synthetase short chain family member2 [Homo sapiens (human)] – Gene – NCBI. www.ncbi.nlm.nih.gov. Retrieved 2018-04-28.

[11] Thombs DL. Introduction To Addictive Behaviors 2ed. London: The Guildford Press. 1999: pp. 64-65.

[12] "Reward system." Wikipedia, The Free Encyclopedia. Wikipedia, The Free Encyclopedia, 6 Oct. 2021. Web. 7 Oct. 2021.

[13] "Ventral tegmental area." Wikipedia, The Free Encyclopedia. Wikipedia, The Free Encyclopedia, 3 Sep. 2021. Web. 7 Oct. 2021.

[14] Ikemoto S (2010). "Brain reward circuitry beyond the mesolimbic dopamine system: a neurobiological theory". Neurosci Biobehav Rev. 35 (2): 129-50.

[15] J. W. Maas, C. L. Bowden, A. L. Miller et al., "Schizophrenia, psychosis, and cerebral spinal fluid homovanillic acid concentrations," *Schizophrenia Bulletin*, vol. 23, no. 1, pp. 147-154, 1997.

[16] Di Chiara G (December 2002). "Nucleus accumbens shell and core dopamine: differential role in behaviour and addiction". Behavioural Brain Research. 2002: 137 (1–2): 75-114.

[17] Soares-Cunha C, Coimbra B, Domingues AV, Vasconcelos N, Sousa N, Rodrigues AJ (19 April 2018). "Nucleus Accumbens Microcircuit Underlying D2-MSN-Driven Increase in Motivation". eNeuro. 2018: 5 (2): ENEURO.0386–18.2018.

[18] Soares-Cunha C, Coimbra B, Sousa N, Rodrigues AJ (September 2016). "Reappraising striatal D1- and D2-neurons in reward and aversion" (PDF). Neuroscience and Biobehavioral Reviews. 2016: 68: 370-386.

[19] Cynthia M. Kuhn, Wilkie A. Wilson. How Addiction Hijacks Our Reward System. Cerebrum Dana foundation. Published April 1, 2005.

[20] How alcohol affects the brain. Web page https://www.soberlink.com//.How Alcohol Affects Different Parts of the Brain | Soberlink.

[21] Grandy DK, Litt M, Alen L, Bunzow JR, Marchionni M, et.al.,. The human dopamine D2 receptor gene is located on chromosome 11 at q22-q23 and identifies a Taql RFLP. Am J Hum Genet. 1989:45(5):778-85.

[22] Cools AR, Van Rossum JM. Excitation-mediating and inhibition-mediating dopamine- receptors: a new concept towards better understanding of electrophysiological, biochemical, pharmacological, functional and clinical data. Psychopharmcologia. 1976; 45(3): 243-245.

[23] Hummel M, Unterwald EM. D1 dopamine receptor: a putative neurochemical and behavioral link to cocaine action. J Cell Physiol. 2002; 191(1): 17-27.

[24] Wright C, Moore RD. Disulfiram treatment of alcoholism. The American Journal of Medicine. 1990; 88(6): 647-55.

[25] Naltrexone Monograph for professionals-Drugs.com. Drugs.com. American Society of Health system Pharmacists. 9 November 2017.

[26] Williams SH. Medications for treating alcohol dependence. American Family Physician. 2005; 72(9): 1775-1780.

[27] Acamprosate oral-Who should not take this medication. WebMD.com. Retrieved 2007-001-08.

[28] Lomas T, Ivtzan I, Fu CH. A systematic review of the neurophysiology of mindfulness on EEG oscillations. Neuroscience & Biobehavioral Reviews. 2015; 57: 401-410.

[29] Springer, S.P. & Deutsch, G. Left brain, right brain: Perspectives from cognitive neuroscience. 2001; New York, New York: W.H. Freeman publishers.

[30] Kabat-Zinn, J. & Davidson, R. J. The Mind's own Physician: A scientific dialogue with the Dalai Lama on the healing power of meditation. 2011: Oakland, CA: New Harbinger Publications.

[31] Holzel et.al.,. Mindfulness practice leads to increases in regional brain gray matter density. Psychiatry Res. 2011. January 30; 191(1): 36-43.

[32] Isralowitz R, Spiegel S, Reznik A, Borkin S, Snir Y. Late life alcohol use and gender differences among Former Soviet Union immigrants. J Ethn Subst Abuse. 2009; 8: 201-205.

[33] Tadic A, Wagner S, Hoch J, Baskaya O, von Cube R, Skaletz C, Lieb K, Dahmen N. Gender differences in axis I and axis II comorbidity in patients with borderline personality disorder. Psychopathology. 2009; 42: 257-263.

[34] Hietala J, West C, Syvälahti E, Någren K, Lehikoinen P, Sonninen P, Ruotsalainen U: Striatal D2 dopamine receptor binding characteristics in vivo in patients with alcohol dependence. Psychopharmacology (Berl) 1994; 116: 28.

[35] Pohjalainen T, Rinne JO, Nagren K, Syvalahti E, Hietala J. Sex differences in the striatal dopamine D-2 receptor binding characteristics in vivo. American Journal of Psychiatry. 1998; 155: 768-773.

[36] Hommer D (2003). Male and female sensitivity to alcohol-induced brain damage. *Alcohol Res Health* 27: 181-185.

[37] Prendergast et al., Do women possess a unique susceptibility to the neurotoxic effects of alcohol? J Am Med Wom. Assoc. 2004; 59: 225-227.

[38] Walter H, Gutierrez K, Ramskogler K, Hertling I, Dvorak A, Lesch OM. Gender-specific differences in alcoholism: implications for treatment. Archives of Women's Mental Health. 2003; 6: 253-258.

[39] Rojiani Rahil, Santoyo Juan F., Rahrig Hadley, Roth Harold D., Britton Willoughby B. Women Benefit More Than Men in Response to College-based Meditation Training. Frontiers in Psychology. 2017; 8: 551.

[40] Crystal Goh. Does gender affect mindfulness?. Does Gender Affect Mindfulness? - Mindful. 2017

[41] Alexander Soutschek et al.. The dopaminergic reward system underpins gender differences in social preferences. n Nature Human Behaviour · November 2017.