



# Addiction and Appetite - Neuro adaptive Mechanisms Affecting Compulsion Over Craving.

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## Abstract

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**Background:** Presently, addiction for excessive eating has been seen in the masses globally due to increased consumption of alcohol, smoking and drugs such as heroin, cocaine and cannabis. Additionally, it will not be astonishing if chocolate, tea, coffee, fast food, etc. are also added in the categories of addictive substances because a high degree of inclination towards these substances can be clearly seen in people. Now, this is emerging as a severe addiction which is badly affecting the health of the people and leading to a myriad number of disorders especially obesity-related health issues. The paper discusses the various apparent similarities in appetite for food and drugs. Research studies suggest that narcotics have a more significant effect than food, particularly with regard to their "desired" neuro-adaptive effects. It is proposed that over-consumption of energy foods causes obesity. It has a negative effect on the human brain and blood flow. When a toxin is absorbed into the bloodstream, it can drive people to lose control of inner desires as well as to crave a harmful chemical. **Conclusion:** This review examines the relationship between the addictive substances and appetite. Many people still use the drug in response, revealing a



variety of pleasurable feelings and unusual behavioral characteristics. Long-term addiction may cause serious consequences for brain injury that can even lead to death.

**Keywords:** Addictive substance, appetite, neuro-adaption, obesity.

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## Introduction

Addiction is defined as the inability of a person to stop consuming an addictive substance or engaging in an activity, and appetite is described as any instinctive desired ability to maintain organic existence, mainly the desire to eat. People used to be addicted to narcotics and alcohol, cocaine, heroin, etc., but they're now getting addicted to common ingredients like, tea, coffee and even fast food). i.e., they are now using common ingredients as addictive substances. According to the data available, globally about 5% of population probably is involved in the use of drugs at least once a day with nearly 0.6% of them being suffering from disorders due to excessive consuming of drugs or related substances<sup>1</sup>. Despite the fact that opioids are the most dangerous variety of cannabis, it is still the most extensively used drug on the planet<sup>2</sup>. Drug users are a disadvantaged group, and the majority of study into their nutritional state points to malnutrition. Drug abuse has been shown to impair nutrition status and body composition by restricting food consumption and nutrient uptake, modifying metabolism, and using various medications, as well as changing the satiety mechanism through hormonal dysregulation<sup>1</sup>. Though during the initial stages of detoxification, i.e., the time when patients are on pharmacotherapy, low food intake is one of the common features observed due to persistent nausea, anorexia, and gastrointestinal disturbances<sup>3,4</sup>. In the first six months of this period, cravings for foods like as sweets, cakes, and other baked goods are common as a substitute for the drug. After six months of detoxifying, structural food consumption and enhanced appetite are common.<sup>4,5,6</sup>

## Literature Survey

### • **Addiction: Brain's reward or self-punishment**

The American Society of Addictive Medicine defines addiction as a fundamental, serious disease of the reward, desire, memory, and related circuitry of the

brain. As a result, addiction is defined by a failure to consistently refrain, a loss of behavioural control, cravings, a lack of recognition of serious behavioural disorders, and a dysfunctional emotional reaction. Addictive behaviors prevail over healthy behaviors related to self-care. Addiction affects neurotransmission, cortical interactions, neuronal circuits, and brain reward structures, so memories of previous rewards (such as food, sex, alcohol, drugs, and the internet) trigger physiological and behavioural responses to external cues, triggering cravings and/or addictive behaviour<sup>7</sup>. According to the American Psychiatric Association (DSM-IV) and the World Health Organization (ICD-10), a person must meet three of the seven criteria listed below in order to be classified as addicted<sup>8</sup>,

- Tolerance
- Withdrawal
- Restricted control
- Detrimental repercussions
- Activities that have been neglected or put off
- Spending a lot of time or effort
- A desire to reduce

Although these characteristics are generally applicable to substance addiction, they have only lately been applied to other types of behavioural addiction, such as drug habit, internet dependency, and addiction to computers and music. One major problem when examining addiction, in particular substance disorder, is that most activities that society defines as harmful might perfectly fulfill the requirements mentioned here<sup>9</sup>. Addiction towards food is not well statistically documented in scientific literature and is not considered under mental disorders (DSM-V) but studies have revealed that, there are eight clinical features often seen in people addicted to food, i.e.<sup>10</sup>

- Having desire to eat yet being satisfied
- Overeating

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- Consuming food till you're packed to the gills
- Repeating the same thing though feeling guilty
- Putting up justifications to give into craving
- Setbacks on previous occasions at setting rules around eating
- Keeping eating habits hidden from others
- Not able to quit unhealthy foods regardless one's own health issues

So, to summarize, food addiction is characterized by eating problems, urges to eat more food, and poor control over food, in spite of the negative consequences of specific foods. The idea of food addiction is diverse and interesting, but it has been shown to be critical in understanding and resolving the obesity epidemic<sup>11</sup>. Alcohol, cigarettes, heroin, and a variety of other substances are prevalent in our culture. Although drug use is linked to sickness, mortality, low productivity, and criminality, the total emotional and societal cost is huge. Addiction is a neuropsychiatric condition characterized by a persistent urge to take a substance despite its negative effects, according to psychologists and psychiatrists. Non-substance addiction has become a new and increasing problem in today's culture, despite the fact that we all are known with drug dependency. Non-substance addiction, like drug addiction, need reward system circuitry. Despite the fact that they are both "addictions," treatment of distinct types of addiction disorders is complicated due to their differences.

- **Appetite: A desire for food with or without hunger**
- **Appetite and hunger**

Appetite is described as a natural urge to satisfy a bodily need, particularly for food; or a strong desire for something, like food. Appetite is regulated by the central nervous system controlled by complex mechanisms. Fasting or postprandial status, determines the release of signals from peripheral locations such as adipose tissue, muscle, liver, pancreas, and stomach to the brain. The related neuronal groups in the hypothalamus that govern appetite activate specific receptors for these signals<sup>12</sup>.

Appetite and hunger are interrelated, although they are not the same thing in scientific terms as hunger is the body's biochemical response to a lack of food. Hunger symptoms include rumbling in the abdomen, sense of vomiting, restlessness, a hollow feeling in the abdomen, drowsiness, trouble in focusing, headache, and so on; whereas specific factors that have been found to increase appetite include boredom, stress, sating their favorite foods, health conditions, medications, ecological influences, and so on. Hunger is influenced by a variety of variables, including lifestyle and health<sup>13</sup>. Appetite physiology is the scientific study of how food, food-related emotions, and food contribute to body homeostasis, body weight, and adiposity. The brain incorporates neural and endocrine signals that encode food taste information, gastrointestinal processes, and metabolic events to create food<sup>14</sup>. When people are anxious, their appetites may increase, leading to an increase in food consumption. Anorexia refers to a lack of desire to eat, whereas orex refers to an increase in appetite.

- **Appetites for foods and drugs: A taste to know**
- 1. **Examination of external cues for food and drug appetite:** It is generally understood that being subjected to certain external influences and sensory stimulation of food are usually linked with feeding which increases one's urge for food as well as appetite. The same signals also produce metabolic responses such as enhanced secretion of saliva, acid reflux, and insulin production. Although their main role may appear to be to prepare the body for food consumption, such reactions may be used to create an increase in hunger, at least in part<sup>15</sup>.
- 2. **Desire to eat:** A strong desire or impulse to consume a certain meal or substance is defined as a food or drug craving, and also refers to a perceptual perception connected to consuming and substance usage. As a result, desire evaluation is based on self-initiated oral reporting of such event and responses to an appropriately phrased assessment scale<sup>16</sup>. To be specif-



ic, substance usage like smoking, and food consumption can occur without appetite. Cravings aren't always connected to eating. We might say "I'm hungry" while expecting a meal or "I was hungry" when clarifying why we eat so much<sup>15,17</sup>.

3. **Tolerance:** Drug tolerance is a reduction in a drug's impact caused by repeated substance exposure, or, in a dose-response effect characteristic, it is a shift to the right, requiring greater dosages to get the similar impact. Tolerance to the stimulating and aversive effects of drug abuse can develop as a result of a variety of adaptive responses, including changes in drug metabolism and regulatory measures, as well as production of established prospective reactions which counterbalance specific therapeutic response<sup>17</sup>.
4. **Withdrawal:** A long voluntary or compelled drug withdrawal can cause adverse effects, such as dysphoria, anxiety, insomnia, fatigue, nausea, muscular ache, autonomy, and take-over sensations. The intensity of the retraction effects varied. The consequences of withdrawal from alcohol and narcotics are the most severe, significantly in the drug class. In terms of maintaining alcohol use including nicotine; escape and avoidance of unpleasant withdrawal symptoms play a key role. Replacement treatment aims to minimize smoking-related withdrawal symptoms. Smoking cessation progress accelerates substantially<sup>15,18</sup>.

In conclusion, some potential differences in food and drug appetites exist in some identifiable features, such as external control of eating pleasure, including certain appetites. Appetite comes with eating, dis-inhibition of dietary restraint, food craving, tolerance to chemical changes in food intake, tolerance to fatigue, and so on. The negative effects of extreme dietary restriction include bingeing on foods, food inclination and desire, where in obesity they even suffer from a reward deficit. etc.,<sup>19</sup>.

- **Control of Appetite: A natural desire to fulfill a need of the body for food**

Appetite control is complicated and poorly understood. The digestive system, endocrine system, and sensory nerves are all connected via control systems to the brain. These strategies are intended to curb hunger, in both immediate and extended periods. Throughout the immediate period it is thought that intestinal sensors control appetite by responding to the direct existence or absence of food, as well as distinct dietary components<sup>20,21</sup>. In response to signals from these sensors, the gut secretes a number of hormones, including ghrelin, which is synthesized by the stomach responding to food restriction and enhances appetite; peptide-YY, which is synthesized by the ileum and colon in order to respond to dietary consumption and inhibits hunger; and cholecystokinin, which is synthesized by the small intestine in response to fat and protein and hinders desire to eat. Insulin is produced by the pancreas in responding to high blood glucose levels, and it also reduces hunger<sup>20,21</sup>. Before, during, and after eating, various hormones are released, influencing feeding behavior and how much is consumed. Appetite can be regulated by the body's composition in the long term. Signaling from fat mass reduce hunger through the hormone leptin, which is produced by adipose tissue<sup>22</sup>. Today's cigarettes are more habit forming than in the past few years due to design changes that have enhanced the strength of nicotine absorption and the nicotine content in tobacco products<sup>23,24</sup>.

- **Drug addiction (Substance use disorder)**
- **Definition:** Substance abuse which can also be stated as drug induced disorder, is a problem that invades a person's brain and behaviour, lacking the ability to control the use of legal or illicit drugs or medications. Even narcotics, such as alcohol, marijuana, and nicotine, are referred to as drugs. Despite the harm that addiction produces, a person can continue to use the substance<sup>25</sup>.



- **Causes:** A variety of variables can influence the development of substance addiction, just as they

can with several psychological problems. Table 1 lists the most important considerations.

Table 1 Factors contributing to drug dependency

| Sl. No. | Factors       | Contribution  |
|---------|---------------|---|
| 1.      | Environmental | In the early utilization drugs; family beliefs, practices, and engagement to a certain community that supports substance use; all play a role         |
| 2.      | Genetical     | After starting to use a substance, inherited (Genetic) traits may influence the development of addiction, slowing or speeding up the disease's course |

- **Impact on Health and Mental Status**
  - **Changes in the brain**
  - Addiction has a variety of effects on the brain. Chemical components in stimulants, nicotine, opioids, alcohol, and sedatives enter the brain and circulatory system after use. Whenever a toxin enters the brain, it has the potential to lead individuals to lack in control of their urges or to want a harmful substance. When someone establishes a substance obsession, their brain is primed for the product's satisfaction. This is due to the brain's reward system being constantly activated. As a result, many people continue to use the substance, which produces a variety of euphoric sensations and odd behavioural patterns. Addiction over a period of time can have serious consequences, including brain damage and even death<sup>26</sup>. When repeated drug use alters the way, brain perceives pleasure and physical addiction develops. Some nerve cells (neurons) in your brain undergo physical alterations as a result of the addictive opioid. Neurotransmitters are substances that neurons utilize to communicate with one another. These benefits might last for a long time after you stop using the drug<sup>26</sup>.
- A. **Drugs' mechanisms of interaction in the brain**
- Drugs alter the way neurons send, receive, and relay signals via neurotransmitters. Because their

chemical makeup matches that of the body's natural neurotransmitter, some medicines, such as marijuana and heroin, can activate neurons. The medications can be added to the nerves and activated by them. While these drugs resemble the chemical compounds of the brain itself, neurons do not trigger the same way as natural neurotransmitters and they contribute to the transmitting of irregular signals utilizing the system. Other drugs, such as amphetamines or cocaine, might cause the release of unusually high amounts of naturally existing nerve transmitters or the avoidance of regular recycling by brain chemical transporters. Natural neural signaling is either amplified or disrupted<sup>18</sup>. To deliver a message, a neurotransmitter releases the connection between the neurotransmitter and the next neuron, or synapse. As a key in the door, the neurotransmitter passes the synapse and attaches to the receiving neuron receptors. This causes the receiving cell to shift. Additional molecules called transporters recycle neurotransmitters (that is, return to their neurons) and restrict or shut the signal between neurons<sup>27,28</sup>.

- **Affected areas of the brain:** Drugs can alter vital parts of the brain that are necessary for survival and can lead to obsessive substance usage, which is reliant and involves brain regions af-



ected by pharmaceutical drugs. The brain is linked by multiple locations and forms complex networks responsible for particular activities, such as concentration, self-regulation, perception, vocabulary, motivation, emotions and action as well as plenty other roles. The basal ganglia, extended amygdala, and prefrontal cortex are three primary areas within the networks implicated in the development and sustainability of illnesses in the usage of drugs<sup>27,28</sup>

- i. **Basal ganglia:** It is important for positive motivation, such as the benefits of healthy behaviours like healthy eating, nutrition, and sex, as well as habit and practice. These areas are a major circuit in the brain's "reward system," and drugs over activate such framework, resulting in intense opioid pleasure. The circuit adapts to the existence of this medication with repetitive treatment, loses sensitivity and finds it impossible to detect joy outside the medication<sup>28</sup>.
- ii. **Extended amygdala:** It contributes to uncomfortable emotions like anxiety, irritation, and restlessness, which signal abduction after the drug's high wears off. This circuit is getting more sensitive as the use of opioids increases. Instead of getting high to receive instant comfort, a person with a drugs addiction needs treatment over time. It also corresponds with the hypothalamus, a part of the brain governed by numerous endocrine glands, including the pituitary gland at the rear of the brain and the surreal gland at the top of each kidney. These glands, in exchange, govern stress reactions and a variety of other bodily functions<sup>27,28</sup>
- iii. **Pre-frontal cortex:** It is situated in face of the brain above the eyes and allows for complicated reasoning functions, which are known as executive functions. The pre-frontal cortex is capable of thought, preparing, managing conflicts, making choices and self-containment of stimulations. Adolescents are the most vulnerable group because of the final section of the brain. Shifting

equilibrium among this circuit and the basal ganglia circuits and enlarged amygdala, compulsively attempt to regulate the opioid by an individual with a substance use problem<sup>27,28</sup>. Specific medicines, such as opioids, have a tendency to interact with other parts of the brain, including the brain stem that controls vital processes including heart rate, breathing, and sleep. This intrusion illustrates why excess doses of breath and mortality can be depressed<sup>27</sup>.

#### ☐ **Co-occurring Nicotine and Other Substance Use and Addiction: The Neurobiological Underpinnings-A survey**

Nicotine use, during puberty, not only encourages the use of harmful tobacco products and raises the danger of nicotine dependency but it also encourages the need for other narcotics and renders the brain more susceptible to the intoxicating effects of addictive substances<sup>23,29</sup>. We realize that using these items by teenagers not only introduces them to nicotine when their brains are still developing and vulnerable to its intoxicating influence, but also stimulates or entrenches smoking tobacco and all of its associated harms, even among those not inclined to smoke<sup>30</sup>. The teenage brain is amazing, and it goes through significant anatomical, functional, and neurochemical changes that allow young individuals to learn and adapt fast. It therefore implies that the teenage brain is much more susceptible to and affected by intoxicants, such as nicotine, and that these effects, particularly those linked to neuronal connection and behavioural control, can persist into adulthood<sup>31</sup>.

#### **Measures to reduce this menace of addiction**<sup>32, 33, 34, 35, 36, 37, 38</sup>

Interventions aimed at teenagers with problematic or dependent substance use must address a number of factors. Stigma and confidentiality are two of them. In some countries, confidentiality cannot be guaranteed since it is legally required that parents, guardians, and occasionally spouses give permission to seek counselling<sup>32</sup>



### Therapy for motivational improvement

Social learning theory and the trans theoretical framework of change are the foundations of motivation enhancement treatment. Through client-centered therapy, it is intended to increase intrinsic motivation for behavioral change. There are various problems to consider when dealing with problematic or dependent substance use in adolescents. Stigma and disadvantage are two of them<sup>34</sup>

CBT (cognitive behavioural therapy)<sup>33</sup> Some research demonstrate that cognitive behavioural treatment (CBT) improves abstinence in tobacco users, while others show that it is effective in cannabis users. According to a recent study, CBT has a low efficacy in the treatment of substance abuse disorders.

For substance abuse, pharmacotherapy is used. Adult alcohol dependence pharmacotherapies, such as naltrexone and acamprostate, are useful in preventing recurrence to heavy drinking<sup>34</sup>. The majority of studies in adolescents focus on drug addiction problem as a result of psychiatric diseases. Lithium has been shown to help young persons with bipolar disorder reduce their alcohol consumption<sup>35</sup>. In juvenile alcoholics, acamprostate was found to be useful in boosting abstinence rates. In young people with alcoholism, naltrexone successfully lowers alcohol cravings.<sup>36,37</sup> Nicotine replacement treatment, bupropion, nortriptyline, and varenicline are all used to help smokers quit<sup>38</sup>

### Conclusion

The main characteristics are "loss of control" and "despite adverse effects," when describing addiction to substances or drugs. Continuing usage of prescribed drugs lead to drug dependency and is considered a form of brain condition induced by prolonged use. While there are no opioid dependencies, the signs and brain processes of drug abuse are somewhat close. Researchers have also often identified and diagnosed the opioid dependency model. Low literacy is related with poorer depressive symptoms in persons with alcohol and drug addiction, however the specific processes underlying the association between literacy and mental health

outcomes should be investigated to inform future intervention efforts<sup>39</sup>. Because the relative prevalence of addiction with other health-related problems has risen in recent decades, owing in part to stigma and a lack of treatment, further study is needed to better understand the impact of mental and addictive diseases in life expectancy changes<sup>40</sup>. Differences between the different addiction/s should therefore not be underestimated and more research are required to identify particular features and neurological pathways underlying various kinds of addiction disorders.

### References

1. Mahboub N, Rizk R, Karavetian M, de Vries N. Nutritional status and eating habits of people who use drugs and/or are undergoing treatment for recovery: a narrative review. *Nutrition Reviews*. 202; 79(6): 627-35.
2. NabipourS ,Ayu Said M , Hussain Habil M. Burden and nutritional deficiencies in opiate addiction: systematic review article. *Iran J Public Health*. 2014; 43(8):1022–1032.
3. Noble C , McCombie L. Nutritional considerations in intravenous drug misusers: a review of the literature and current issues for dietitians. *J Hum Nutr Diet*. 1997; 10: 181–191.
4. Neale J, Nettleton S, Pickering L , et al. Eating patterns among heroin users: a qualitative study with implications for nutritional interventions. *Addiction*. 2012;107(3):635–641.
5. Stickel A, RohdemannM, LandesT , et al. Changes in nutrition-related behaviors in alcohol-dependent patients after outpatient detoxification: the role of chocolate. *Subst Use Misuse*. 2016;51(5):545–552.
6. Cowan J, Devine C. Food, eating, and weight concerns of men in recovery from substance addiction. *Appetite*. 2008; 50:33–42.
7. ASAM (2016) <http://www.asam.org/for-the-public/definition-of-addiction>
8. Psychology Today (2015) <https://www.psychologytoday.com/basics/addiction>

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9. Shaffer HJ, Hall MN, Vander Bilt J. Estimating the prevalence of disordered gambling behavior in the United States and Canada: a research synthesis. *Am J Public Health*. 1999; 89(9):1369-76.
10. Dimitrijević I, Popović N, Sabljak V, Škodić-Trifunović V, Dimitrijević N. Food addiction-diagnosis and treatment. *PsychiatraDanubina*. 2015; 27(1):0-106.
11. Phillips G.O, Williams P.A. *Handbook of Hydrocolloids*. 2<sup>nd</sup> ed. Woodhead Publishing Series in Food Science, Technology and Nutrition 2009;50-8
12. <https://www.medicalnewstoday.com/articles/appetite>
13. *Encyclopedia of Human Behavior*. 2<sup>nd</sup> ed. 2012; Pages 187-198.
14. Rogers PJ. Eating habits and appetite control: a psychobiological perspective. *Proc Nutr Soc*. 1999; 58(1):59-67.
15. Rogers PJ, Smit HJ. Food craving and food "addiction": a critical review of the evidence from a biopsychosocial perspective. *PharmacolBiochemBehav*. 2000 May; 66(1): 3-14
16. Altman J, Everitt BJ, Glautier S, Markou A, Nutt D, Oretti R, Phillips GD, Robbins TW. The biological, social and clinical bases of drug addiction: commentary and debate. *Psychopharmacology (Berl)*. 1996 ;125(4):285-345.
17. Koob GF, Volkow ND. Neurobiology of addiction: a neurocircuitry analysis. *Lancet Psychiatry*. 2016;3(8):760-773.
18. Rogers PJ. Food and drug addictions: Similarities and differences. *PharmacolBiochemBehav*. 2017 Feb; 153:182-190.
19. Pilgrim AL, Robinson SM, Sayer AA, Roberts HC. An overview of appetite decline in older people. *Nurs Older People*. 2015 Jun;27(5):29-35.
20. Parker BA, Chapman IM. Food intake and ageing-the role of the gut. *Mech Ageing Dev*.2004 Dec;125(12):859-66.
21. Blundell JE, Caudwell P, Gibbons C, Hopkins M, Naslund E, King N, Finlayson G. Role of resting metabolic rate and energy expenditure in hunger and appetite control: a new formulation. *Dis Model Mech*. 2012 Sep;5(5):608-13.
22. Facing Addiction in America: The Surgeon General's Report on Alcohol, Drugs, and Health [Internet]. Substance Abuse and Mental Health Services Administration (US); Office of the Surgeon General (US). Washington (DC): US Department of Health and Human Services; 2016 Nov.
23. Land, T., Keithly, L., Kane, K., Chen, L., Paskowsky, M., Cullen, D., et al. Recent increases in efficiency in cigarette nicotine delivery: implications for tobacco control. *Nicotine & Tobacco Research*. 2014; 16(6): 753–758.
24. Mayo Clinic. Drug addiction (substance use disorder) [internet] <https://www.mayoclinic.org/diseases-Conditions/drug-addiction/diagnosis-treatment/drc-2036513>
25. Addiction center. Addiction and the brain. <https://www.addictioncenter.com/addiction/Addiction-brain/#:~:text=Addiction%20impact%20the%20brain%20on,or%20crave%20a%20harmful%20substance.>
26. NIDA. "Drugs and the Brain." *National Institute on Drug Abuse*, 10 Jul. 2020, <https://www.drugabuse.gov/publications/drugs-brains-behavior-science-addiction/drugs-brain> Accessed 27 Sep. 2020.
27. Abuse S, US MH, Office of the Surgeon General (US). Facing Addiction in America: The Surgeon General's Report on Alcohol, Drugs, and Health [Internet].
28. Jamal A, Gentzke A, Hu SS, Cullen KA, Apelberg BJ, Homa DM, King BA. Tobacco Use Among Middle and High School Students - United States, 2011-2016. *MMWR Morb Mortal Wkly. Rep*. 2017 ;66(23):597-603.
29. Soneji S, Barrington-Trimis JL, Wills TA, Leventhal AM, Unger JB, Gibson LA, Yang J, Primack BA, Andrews JA, Miech RA, Spindle TR, Dick DM, Eissenberg T, Hornik RC, Dang R, Sargent JD. Association Between Initial Use of e-Cigarettes and Subsequent Cigarette Smoking Among Adolescents and





- Young Adults: A Systematic Review and Meta-analysis. *JAMA Pediatr.* 2017; 171(8):788-797.
30. Yuan M., Cross S. J., Loughlin S. E., Leslie F. M. Nicotine and the adolescent brain. *Journal of Physiology.* 2015; 593(16): 3397–3412.
31. Bryant J, Bonevski B, Paul C, McElduff P, Attia J. A systematic review and meta-analysis of the effectiveness of behavioural smoking cessation interventions in selected disadvantaged groups. *Addiction.* 2011;106:1568-85.
32. Jensen CD, Cushing CC, Aylward BS, Craig JT, Sorrell DM, Steele RJ. Effectiveness of motivational interviewing interventions for adolescent substance use behavior change: A meta-analytic review. *J Consult Clin Psychol.* 2011; 79: 433-42.
33. Jonas DE, Amick HR, Feltner C, Bobashev G, Thomas K, Wines R, et al. Pharmacotherapy for adults with alcohol use disorders in outpatient settings: A systematic review and meta-analysis. *JAMA.* 2014;311:1889-900.
34. Clark DB. Pharmacotherapy for adolescent alcohol use disorder. *CNS Drugs.* 2012; 26: 559-69.
35. Minozzi S, Amato L, Davoli M. Maintenance treatments for opiate dependent adolescent. *Cochrane Database Syst Rev.* 2009; 15 (2).
36. Jiloha RC. Pharmacotherapy of smoking cessation. *Indian J Psychiatry.* 2014;56:87-95.
37. Gilmore AS, Rodriguez N, Webb VJ. Substance abuse and drug courts: The role of social bonds in juvenile drug courts. *Youth Violence Juv Justice.* 2005; 3:287-315.
38. Lincoln A, Paasche-Orlow MK, Cheng DM, Lloyd-Travaglini C, Caruso C, Saitz R, Samet JH. Impact of health literacy on depressive symptoms and mental health-related: quality of life among adults with addiction. *Journal of general internal medicine.* 2006; 21(8):818-22.
39. Rehm J, Shield KD. Global burden of disease and the impact of mental and addictive disorders. *Current psychiatry reports.* 2019; 21(2):1-7.

