The Predisposed Brain: A Review

Ritika Sharma¹, Amanpreet Kaur Dhindsa²,

Assistant Professor, University Institute of Pharmaceutical Sciences
University Institute of Pharmaceutical Sciences.

ABSTRACT
The addicted brain is physiologically and chemically distinct from the normal brain. Predisposition is fanatic thinking and neurotic need for alcohol, drugs, food etc. in defiance of negative ramifications, addiction appends development of tolerance, withdrawal symptoms, physical cravings and infatuation. Breaking the cycle of addiction means changing behaviours, which further happens in stages:pre-contemplation, contemplation, preparation, action and maintenance with a proper relapse. A large volume of published literature over the last few decades debar a comprehensive review. The addiction of the brain and its broad biological profile has attracted the attention of many researchers to explore this realm of interest. This article presents a comprehensive review of addiction of pharmacological drugs and their effect on the human brain.

1. INTRODUCTION
There are some classes of drugs that are known to cause addiction. They include alcohol, tobacco (contain nicotine), caffeine (widely used as psychoactive substance), marijuana, inhalants (often solvents found in glue or gasoline), opioids, psychostimulant groups (cocaine, amphetamine, methamphetamine) and hallucinogens (PCP, phencyclidine, LSD).

Dependance v/s Addiction
Dependence is a state of chronic drug-taking where withdrawal is experienced when the taking of drug is stopped. Whereas, addiction is the behaviour of seeking and taking drugs such that there are negative consequences in life.

*Drug use: a serious problem*

The prefrontal cortex is important for our function. It is believed to enhance activity. It is also involved in emotional regulation. The predisposition of drugs greatly affects this area. The estimated economic cost of society due to illegal drugs is over $180 billion a year.

SUBSTANCE USED OVER A LIFETIME AMONG PERSON AGED 12 OR OLDER

<table>
<thead>
<tr>
<th>DRUG</th>
<th>LIFETIME</th>
</tr>
</thead>
<tbody>
<tr>
<td>ALCOHOL</td>
<td>82.5</td>
</tr>
<tr>
<td>TOBACCO PRODUCTS</td>
<td>68.8</td>
</tr>
<tr>
<td>MARIJUANA</td>
<td>42.0</td>
</tr>
<tr>
<td>COCAINE</td>
<td>18.3</td>
</tr>
<tr>
<td>HALLUCINOGENS</td>
<td>14.8</td>
</tr>
<tr>
<td>PRESCRIPTION PAINKILLERS</td>
<td>13.8</td>
</tr>
<tr>
<td>INHALANTS</td>
<td>8.6</td>
</tr>
<tr>
<td>METHAMPHETAMINE</td>
<td>5.1</td>
</tr>
<tr>
<td>SEDATIVES</td>
<td>3.0</td>
</tr>
<tr>
<td>HEROIN</td>
<td>1.6</td>
</tr>
</tbody>
</table>

ESTIMATED COST TO SOCIETY

Illegal drugs: $181 billion/year
Alcohol:$185 billion/year
Tobacco:$193 billion/year
Total:$559 billion/year

*Behavioural addictions-*

While some individuals feel that non-substance use deportment can be an addiction, a behaviour can be orderly called a disorder or an addiction only if there are careful scientific studies that support that idea. Some of the institutes that carry the study of drug addiction are:

- NIDA- National Institute on Drug Abuse
- ONDGP- Office of National Drug Control Policy
- NIAAA- National Institute on Alcohol Abuse and Alcoholism
- SAMHSA- Substance Abuse and Mental Health Services Administration

*Drug Dynamics -*

The drug reaches the brain via blood. Drug dynamics is all about what happens to the drug in the body. When the drug is given orally it has to be absorbed from the stomach and intestines into the blood and from the blood it crosses the blood-brain barrier and reaches the brain and shows its effect. Drugs which are injected directly into the bloodstream are not absorbed by the stomach but are still passed into the brain. Nicotine/inhalants are absorbed directly from the air in the lungs to the blood. Further, drugs are metabolised or changed which can result in cessation of action. The step of metabolism takes place in the liver. The next and final step after metabolism is excretion, which includes clearance through urine or faeces. The second elimination includes a half-life of drug which is the measure of the rate of removal of the
drug, its time needed to remove or metabolize 50% or half of the drug. Eg.- ethanol, which is metabolised at a steady rate than fractional rate. One of the pragmatic impacts of the drug being excreted in urine is that drug screen tests have been developed to screen for the presence of the drug in urine. Sometimes, the quarry of drugs can be the metabolites of drugs.

**Detecting drugs in the body**-

The detection of drugs in the body is done by two measures: screens and tests. Screens are the broad assay that looks for many different drugs. Tests on the other hand are assays that are very specific and rigorous. Normally, many different drugs with similar shapes might be spotted or react in the assay that is the reason we call them screens. One example of the assay is the antibody detection assay. Where the shape of a drug molecule is detected by the antibodies that bind to it. The tests that are carried are either blood tests or urine tests. The types of equipment used in these tests are chromatographs or mass spectrometers. These assays have a detection window that depends on copious intermediaries like how well the drug was absorbed in an individual and was the drug metabolised. The screen may also pivot on detecting a metabolite of drug. As metabolites have a longer half-life. Example- cocaine metabolite takes detection time of 2-5 days, marijuana metabolite takes 30-60 days in chronic users and morphine if injected directly takes 2-4 days. Screens are mostly used because they are less expensive and are more rigorous and reliable chemical tests.

**Synaptic transmission- the target of addicting drugs**-

Synaptic transmission is the same as neurotransmission. It is the process that occurs in the brain and is fundamental to how the brain works. Neurons are uniquely shaped cells tailor-made for an organ like brain. Neurotransmission occurs in three major steps: 1) release of neurotransmitters, 2) receptor interactions, 3) removal from receptors. Neurotransmitters (stored in vesicles inside nerve terminal) sets off signals that are critical for the working of the brain. Therefore, evolutionary forces have developed a mechanism to control the disposition of neurotransmitters. when action potential or nerve impulse annex the nerve terminal the vesicle fuse with the membrane of nerve terminal and release content into the synaptic cleft. Drugs alter the neurotransmission. Receptors are the molecule sites where neurotransmitters adhere to. Examples of receptors can be- 1) GPCR- G protein-coupled receptors which result in metabolic and biochemical changes in the neuron. 2)ion channel receptors- they result in changes in charge distribution. Cocaine and nicotine directly/indirectly mimic neurotransmitters. The dopamine is synthesised and is then stored in vesicles which are further released and interact with receptors. Further, it is removed from receptors by reuptake. When cocaine is at a dopaminergic synapse it plug the transporter which blocks the removal of dopamine from the synapse. This affects the high level of dopamine in synaptic space and increases the level of receptor stimulation. Cocaine exerts its action by binding to and blocking the dopamine transporter. When the transporter is blocked, dopamine can not be removed and its level increases exorbitantly causing the receptors to be stimulated gravely. Acetylcholine binds to ion channel receptors, opening the channel and allowing the flow of ions and that affects the neuron. Nicotine works same as acetylcholine. Acetylcholine is broken down by acetylcholinesterase to acetate and choline which is further broken down to inactive products. Neurotransmitter has a duration of action of a fraction of seconds. The brain has multiple receptors because of multiple locations. The difference between neurotransmitter and drugs is that neurotransmitters have a very rapid duration of action and levels are controlled by brain mechanism and the function of the brain is normal. Whereas, in case of drugs the duration of action is long-lasting and determined by the half life in blood and might cause distorted brain functions.
Case: cocaine-
In 1880s European physician, Sigmund Freud studied cocaine. The study showed that restorative or stimulant effects of cocaine were so contrasting to the depressant effects of alcohol, he thought it could be an antidote to alcoholism. But, cocaine addiction caused more problems. Cocaine is said to be the “third flail of mankind” after alcohol and opium.

Drugs are pliant-
The lone drug can do many things by acting at many different molecular sites or receptors. Predisposed drugs can be benign in some ways and very toxic in others. The shape of the drug should be gratis to the shape of the receptor. As said in a common analogy ‘it should fit like lock and key’. For the drug to have its influence it should fist bind to the receptor. The drug can do a variety of things, for example, cocaine can: reduce bleeding, produce euphoria, cause addiction, act as a local anaesthetic. Receptors are extensively distributed. Drugs and their metabolites are frequently excreted in urine and blood. There are urine screens where the goal is simply to detect the presence of a given drug or a class of drug. It is often used in antibody detection procedures. A confirmatory test is often done with very sophisticated equipment generally gas chromatograph or mass spectrometer.

ALCOHOL-
In US alcohol ranks third in malady. It impacts 8 million dependent drinkers. All cases of liver ailment are associated with alcohol. It is also a leading cause of disquieting injuries. (NIAAA) national institute for alcohol abuse and alcoholism recommends no more than 14 drinks per week for men and 7 drinks per week for women as women tend to be more sensitive to the effects. Effects of alcohol intake include loss of muscle coordination, changes in mood, personality and behaviour change, mental impairment, obvious intoxication, coma and sometimes death. The withdrawal symptoms related to the same include tremor, insomnia, nausea or vomiting, hallucinations, anxiety and agitation and seizures. Ingestion of alcohol causes the release of dopamine in reward areas of the brain. The opioid system is involved in this. Alcohol increases the action of GABA which inhibit neurotransmitter and blocks glutamate receptor and NMDA receptor.

Nicotine –
It is responsible for the repeated use of tobacco. Some pros of nicotine include cognitive enhances, improved attention, memory and computational abilities, improved moto abilities.
Whereas, the cons include product dependence, chronic smoking, premature deaths, reduced life span, chronic obstructive pulmonary disease, lung cancer, CVD. The nicotine receptor is the same as the receptor of acetylcholine which is a neurotransmitter. It is composed of bundles of subunits (alpha and beta-type). Nicotine in blood enters the brain quickly and binds to the receptor and opens the ion channel. It leads to an influx of sodium ions and efflux of potassium ions and the influx of calcium ions. Dopamine release is increased in the prefrontal cortex. Nicotine can produce relaxation, drug stress and cause activation which leads to an increase in blood pressure. Further, it leads to schizophrenia, depression, ADHD, irritability, frustration, anger, anxiety, dysphonia, depression. Treatment can be done by E-cigarettes which contains a vapourised nicotine solution and eliminates smoke toxicity. However, the risk is uncertain.

Marijuana-
It is obtained from Cannabis sativa or Cannabis indica. It contains a mind-altering substance called cannabinoids - Tetrahydrocannabinol (THC) and cannabidiol (CBD). The effects of cannabinoids include impaired memory, impact on judgement, memory, balance and problem-solving. Along with this it also creates calm and euphoria state, pain and nausea, weight loss in AIDS, induce transient schizophrenia-like symptoms in healthy individuals. Marijuana works by interacting with endogenous substances in the brain. Endocannabinoids have a common function that inhibits the release of another neurotransmitter in retrograde action. There are two cannabinoid receptors - CB1 (in brain), CB2 (periphery). They both are G protein-coupled receptors. Endocannabinoids are broken down by fatty acid amide hydrolase (FAAH) and monoacylglycerol lipase (MAG).

Psychostimulants –
This category of drugs includes cocaine, crack, methamphetamine. Cocaine causes vasoconstriction and acts as a local anaesthetic. Methamphetamine is FDA approved in the treatment of ADHD and narcolepsy (a sleep disorder). It can be ingested orally, snorted or injected. It provides faster entry to the brain and there are most reinforcing and addicting ways of taking drugs. Cocaine Is obtained from Erythroxylum coca it is an HCl salt that vapourises at 190degree Celcius. Crack is the same as cocaine but vapourises at low
temperature (90-degree Celcius). It can be smoked. Amphetamine has a much larger duration than cocaine as it has a larger half-life. It blocks dopamine transporter and releases dopamine. Amphetamine acts as stimulants, hallucinogens, creates a sense of euphoria, confidence, increases sexual performance, increase sensory awareness and interfere with sleep. The chronic effects include producing psychic disorder, dependence and dysphoria.

**Hallucinogens**

These are the drugs that alter consciousness by inducing sensory and peripheral distribution. They are of two types: 1) phencyclidine PCP or angel dust. It is similar to ketamine. These compounds are called dissociative anaesthetics as they produce a feeling of separation of mind from the body. It can cause schizophrenic like state, psychosis and catatonic. 2) LSD- it have sometimes lead to suicide. It can cause persistent perceptual expression. It acts on serotonin receptor 2A. it is used in psychotherapy. Hallucinogens cause disorientation, confusion, hallucinations, delusion, comma. PCP interferes with major excitatory neurotransmitter glutamine and inhibits its function causing NMDA receptor blockage.

**Opiate drugs**

They are produced from morphine which is the compound found in the poppy plant. The effects of opiate drugs include a reduction in pain, it helps in production of euphoria, relief from constipation, causes sweating, mental confusion, tremour, slow breathing, constricts the pupil, diarrhoea and vomiting.it works by stimulating opiate receptors.

**Sedatives/Antianxiety/Hypnotics**

These are the drugs that cause calming effect, reduce anxiety and facilitate sleep. Can be categorised into 1) benzodiazepines- Xanax, Valium 2) non benzodiazepines- zolpidem,
Ambien. Benzodiazepines that are commonly used are Valium, Xanax, ativan and Klonopin. They work by inhibiting or blocking the GABA receptor.

\[
\text{benzodiazepine}
\]

**Inhalants**-
These are usually the liquids or gases and the fumes are inhaled so that they can show their effect. They are found in paints, glues, etc. inhalants are a sundry group of substances as they are distributed or classified on the fact of them being volatile or gaseous. The first group is of solvents which includes glues, paint thinners, motor fuels, nitrous oxide (laughing gas), alkyl nitrates (found in room deodorizer), propellents like hair spray, fuels, cigarette lighter fluid. The first time effects comprise of excitation, depression produces apparent drunkenness caused by disruption of mental processes, loss of coordination, slurred speech. They also irritate eyes and lungs, increased concentration can produce hallucinations, seizures, coma and death. The second group includes anaesthetics which cause GABA-A and glycine receptor inhibition and results in relaxation, anaesthesia and amnesia. Stress is a common factor in drug abuse. The long term effects include brain damage and shrinkage in some areas. The mechanism of action occurs as toluene that is found in paint thinners cause generalized depression of the brain by inhibiting excitatory neurotransmitter receptors. Nitrous oxide inhibits NMDA receptor. The treatment comprises of discontinuation, symptom treatment and counselling as there are no proven medications yet.

\[
\text{Toluene} \quad \text{nitrous oxide} \quad \text{trichloroethylene}
\]

**Caffeine**-
It comes under the grouping of mild stimulants. It is a psychoactive drug and alters the way mind functions. It leads to abuse, tolerance and addiction. The withdrawal symptoms may include restlessness, nervousness, insomnia, tachycardia, frequent urination and muscle twitching. An abrupt stop may cause headache, depression, fatigue, drowsiness and unpleasant mood. Caffeine attaches with neurotransmitter adenosine and antagonises at two severe adenosine GPR receptors and increase dopamine activity in them. Caffeine is inversely proportional to adenosine and its working. Adenosine inhibits the release of other neurotransmitters and decreases excitation along with a decrease in locomotion act and a decrease in the action of the heart.
New and other substances-
These include anabolic steroids, natural products and bath salts. Anabolic steroids are derivates of testosterone. They promote the growth of skeletal muscle and promote the growth of male sexual characteristics. The receptors are testosterone. The adverse reaction includes abnormal breast development in men, heart attack, liver cancer and testicular shrinkage. Natural products include nuts betel (cause mild euphoria) and kava (pacific pepper plant). Bath salts are composed of mephedrone, cathinone. They produce the feeling of ecstasy. the compounds included in them are mephedrone and pyrovalerone.

Animals in drug addiction research-
Certain sets of rules are to be considered before animal testing like the committee will require the study that is nontrivial and helpful, discomfort o any brute be cut back on, and they should be trained to assess important outlook. Best animal models should be selected. They should produce outcomes that are or close to the ones that have been formerly found in humans. This certifies the model, produce results that are anticipated to apply on humans intime ahead, PhD level scholar to be selected. Animal models are further branched into-

1) drug self administration
2)conditioned place preference.

animal model of drug self-administration – in this mode the researchers inject the animals with the drug. the catheter enters the animal through the skin on the back and is placed inside the jugular vesicle. Animals are presented with two levers the first one is responsible for the delivery of drug like cocaine. The second one is responsible for the delivery of saline or water. The animal quickly learns which one is the lever for cocaine and presses it. Whereas, the second one is completely ignored. The dose-response curve is noted.

Conditioned place performance (CPP)- The injected animal is placed inside a 2-3 chambered box. the photocell in the box measures time how much does animal spend in a particular chamber. The first is the training phase and the second is the testing phase. This method is simple as animal surgery is not required and the testing apparatus is simple. There is the identification of either awarding or assertive substances. Electrical barrier gives simulation reward.
Dopamine and natural rewards-
Reward circuits in the brain are critical for the survival of our kind. It makes us elated when we do something good for our survival. Drugs operate a very strapping reward system. Nucleus accumbens receive dopamine-containing nerve terminals. Cocaine blocks removal of dopamine from the synapse and thereby elevating the levels of dopamine at the receptors. Sexual activity as an example of mesolimbic dopamine system which is the least art of reward system. Cocaine administered results in an elevation of synaptic dopamine in the nucleus accumbens. Cocaine blocks the dopamine transporter and results in a massive synaptic elevation in dopamine levels.

Neuroplasticity and how drugs can change the brain-
The brain is neuroplastic i.e. it can change its structure, signalling and gene expression. Generally, neuroplastic changes build-up or weaken signalling in specific neuronal circuits due to changes in the synapse to the formation of the new synapse. Drugs change the shape and structure of the brain as well as functions of neurons. The drug induces neuroplasticity can be accomplished by activating transcription factors or by epigenetic mechanisms.

How drugs alter gene expressions-
Signalling and epigenetics
Genes are code for proteins which are found in DNA. DNA is referred to as transcription and splicing (ensures that RNA is in the correct length) along with that it acts as a template for producing mRNA. Regulation of gene expression results in regulating protein levels by neurotransmitter reduction. DNA is controlled by a group of proteins that include transcription factor. A common upshot of G protein signalling is to activate transcription factors by phosphorylation. Once the G Protein, through reverse activates Transcription factor it can build to the regulatory regions of the DNA, and levels of RNA and protein in the cell can be changed.

Self-medication and comorbidity-
Self-medication is the use of the drug by an addict to allay the discomfort of the existing problematic situation other than the problem of addiction. Co-morbidity is a situation in which two or more disorders or problems exist in the same person and disorders can interact or maybe make it worse. Stress promotes continuous and relapsed drug use.

Prevention and treatment-
Set of activities such as taking medications or changing behavioural expertise it cab vary as the drug problem itself. An attitude associated with addiction is mainly cruel and that of
disgust. It is mainly due to lack of awareness, rationality and information. Medication for opiates includes methadone, buprenorphine, naltrexone. For tobacco addiction nicotine patch, spray gum and lozenges can be used. In the case of smoking bupropion and varenicline are prescribed naltrexone, acamprosate and disulfiram are taken in case of alcohol addiction.

REFERENCES-


[41] Zhao Y, Dayas CV, Aujla H, Baptista MA, Martin-Fardon R, Weiss F. Activation of group II metabotropic glutamate receptors attenuates both stress and cue-induced ethanol-seeking and modulates c-fos expression in the hippocampus and amygdala. The Journal of Neuroscience. 2006;26(39):9967–9974. [PMC free article] [PubMed] [Google Scholar]
